Nephrology consult in toxicology

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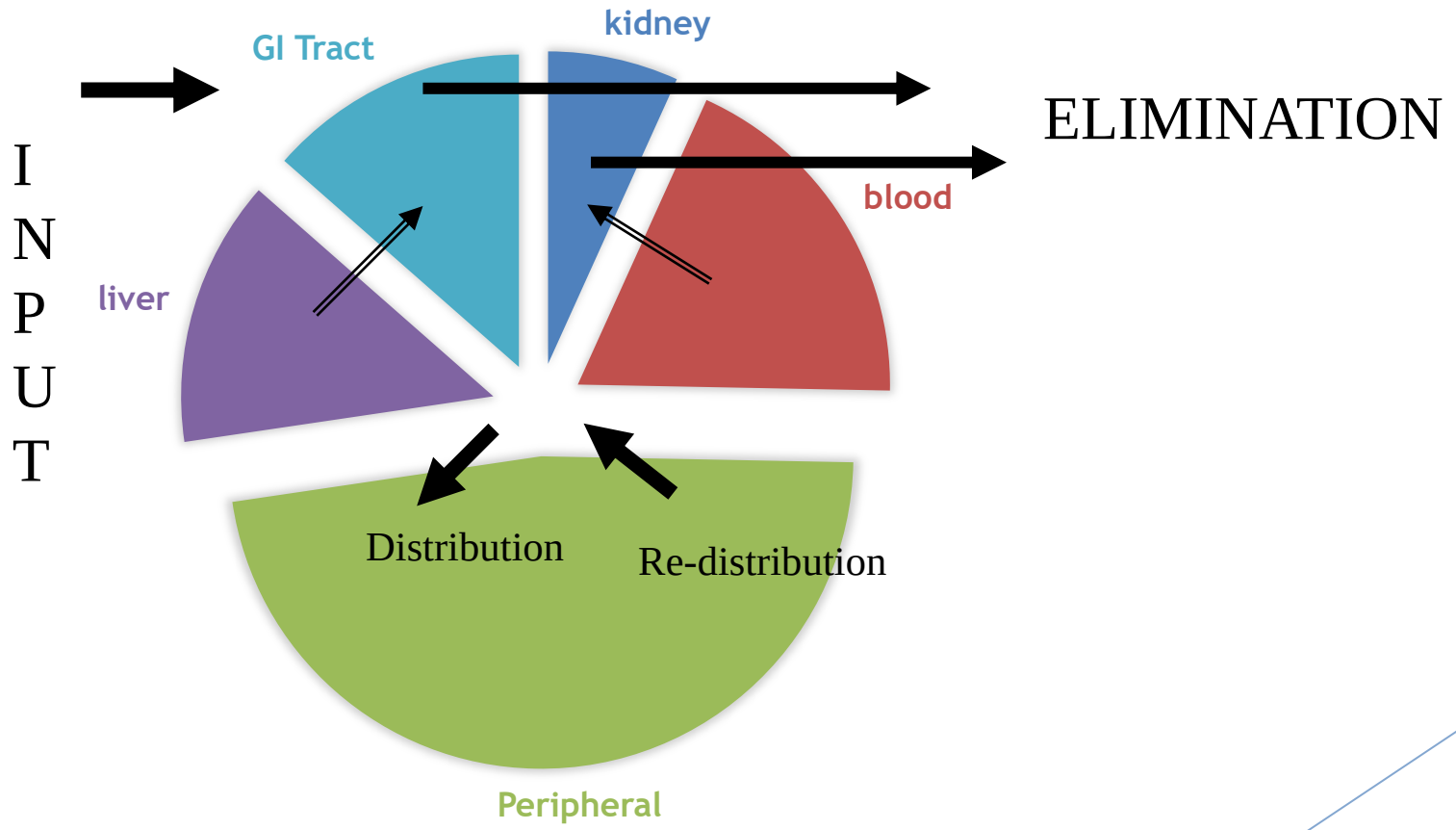
Head of the Rational Prescribing and Consumption Group and Information on Health Products of FDA:

- Overall, drug poisoning, including methadone, tramadol, and other drug poisonings, killed 2,376 people last year and 1,062 in the first five months of this year. Death due to drug poisoning in our country, after death due to poisoning and substance abuse and having 28 to 31% of all deaths in this area is in second place.

- The head of the Food and Drug Administration's rational prescribing and consumption group, and information on health products, explained about the drugs that most often lead to poisoning: Antidepressants and antipsychotics, followed by non-narcotic analgesics, are responsible for nearly 70% of drug poisoning cases. Poisoning with non-narcotic analgesics, such as acetaminophen, is more common in children than in adults.

PHARMOCOKINETIC COMPARTMENTS



Elimination

- Corporeal: Augment physiological process.
- Extracorporeal (ECTR):Which required an artificial device located outside the body.

Poisons whose elimination may be elimination enhanced by corporeal techniques

Urine alkalization	Multiple dose activated charcoal	Na polystyrene sulfate	Purssian blue
Salicylate Methotrexate Chlorpromamide Phenobarbital	Carbamazepine Colchicine Dapsone Phenobarbital Phenytoin Quinidine Salicylate theophylline	Lithium potassium	Radiocesium Thallium

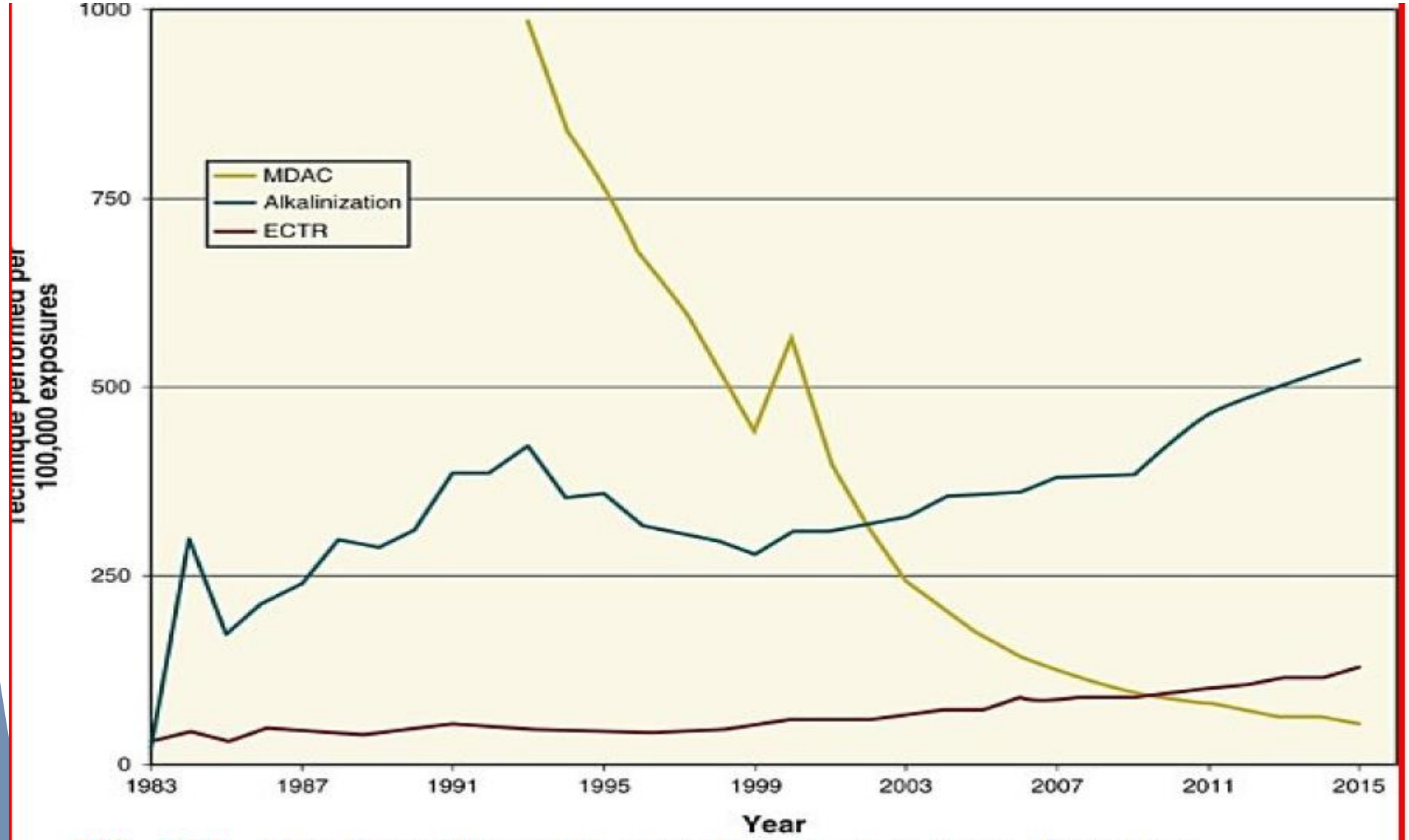


FIG. 67.1 This figure illustrates how often these various elimination enhancement techniques were used in the United States from 1983 to 2015. *ECTR,* Extracorporeal treatment; *MDAC,* multiple-dose activated charcoal.

EXtracorporeal TReatment In Poisoning

In 2010 a multidisciplinary and multinational collaborative known as(EXTRIP work group) aimed to clarify the role of ECTRs in clinical practice through the development of evidence base systemtic review - and expert opinion–based recommendations.

The executive summaries of all EXTRIP recommendations are published at http://www.extrip-workgroup.org/recommendations according the level of recommendation. For tricyclic antidepressants and digoxin, the adverse effects of ECTR were considered to outweigh any potential benefit of ECTR.

Recommended criteria for ECTR:

- Severe toxicity with life-threatening condition such as hypotension, coma, resistant metabolic acidosis, respiratory depression, unstable cardiovascular conditions and cardiac dysrhythmia.
- Natural removal mechanisms impaired, such as kidney or liver or heart failure
- Ingestion of a toxin with serious delayed effects such as methanol, ethylene glycol, paraquat, acetaminophen.
- Removed by dialysis faster than its natural excretion from the body, total body elimination increased by 30%,endogenous clearance <4 ml/min/kg.
- Absence of preferable altenative treatments.
- Reduce ICU or hospital length ,without change in outcome.

Principle and factors influencing poison removal during ECTR

$$\text{EXTRACTION RATIO (ER)} = (A-V)/A$$

A:inflow(or prefilter)plasma.

V:outflow (or postfilter) plasma.

ER=1 means complete removal.

$$CL_{ECTR} = Q_B * (1-H_{CT}) * ER$$

QB:Blood flow

Hct:hematocrit

Poison related factors

The primary determinants of poison removal(dialyzable) by ECTR are :

- molecular weight (MW)
- volume of distribution (V_D)
- hydro- and lipophillicity
- protein and tissue binding
- endogenous clearance<4cc/min/kg

Extrcorporeal (ECTR)

Methode	process	MW(dalton)	Pr.bind	complication	comment
HD	Diffusion	<10,000	<80 %	+	Correct Acidemia, Uremia, Electrolyte
HF	convection	<50,000	<80%	+	#
HP	adsorption	<50,000	<95%	+++	Saturation cartridge
CRRT	Convection and/or Diffusion	<10,000-50,000		+	Correct Acidemia, Uremia, Electrolyte
PD	Diffusion	<500-5000	<80%	++	Low efficacy
TPE	Centrifigurat ,separate Filtrate	<1,000,000	None	+++	
Albumin dialysis	Diffusion adsorption	<60,000-100,000	<95%	++	Liver Replacement support

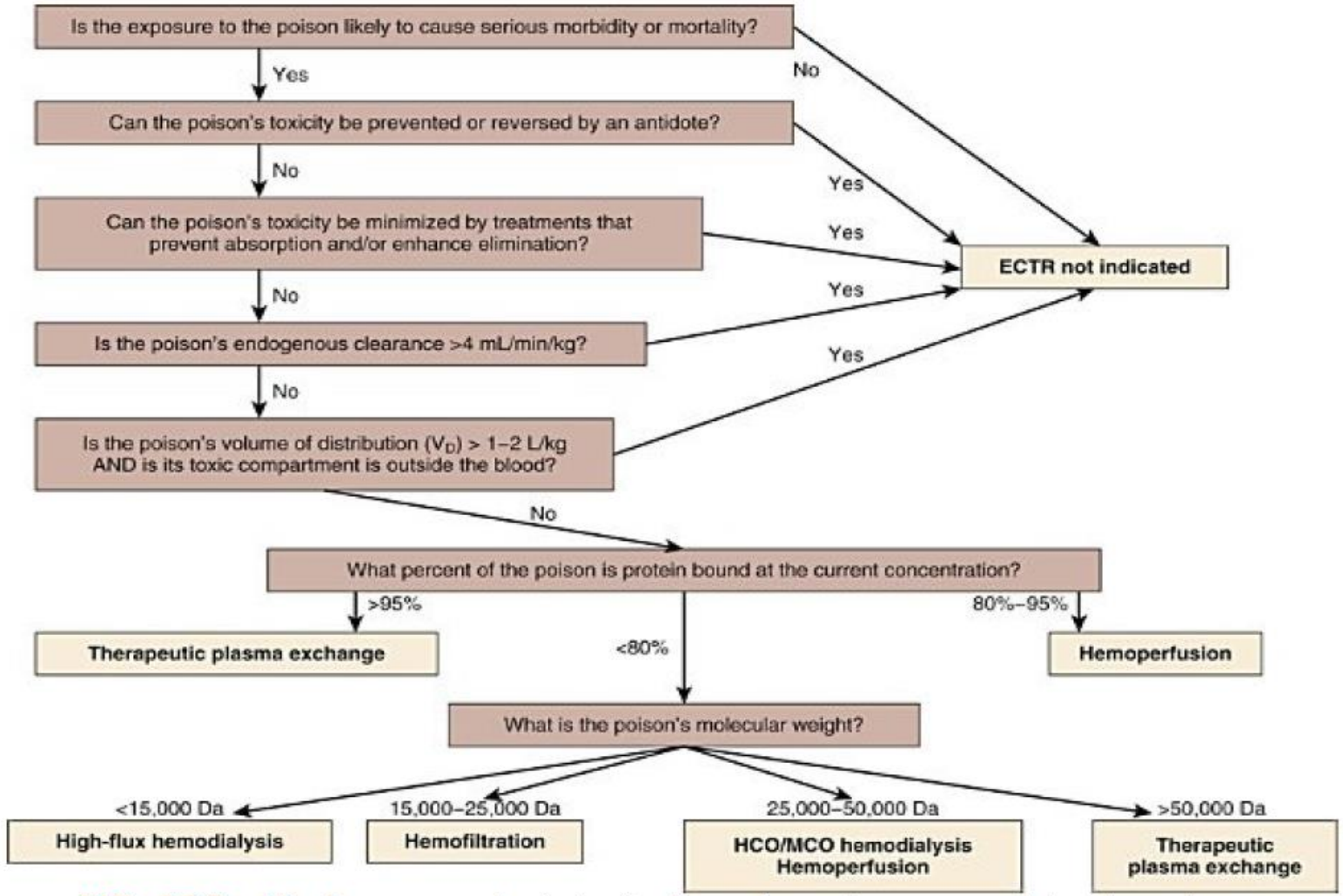


FIG. 67.3 Most common toxin indications for extracorporeal treatments. *ECTR,* Extracorporeal treatment; *HCO,* high cut-off; *MCO,* medium cut-off; V_D, volume of distribution. (Adapted with permission from *Seminars* of dialysis.)

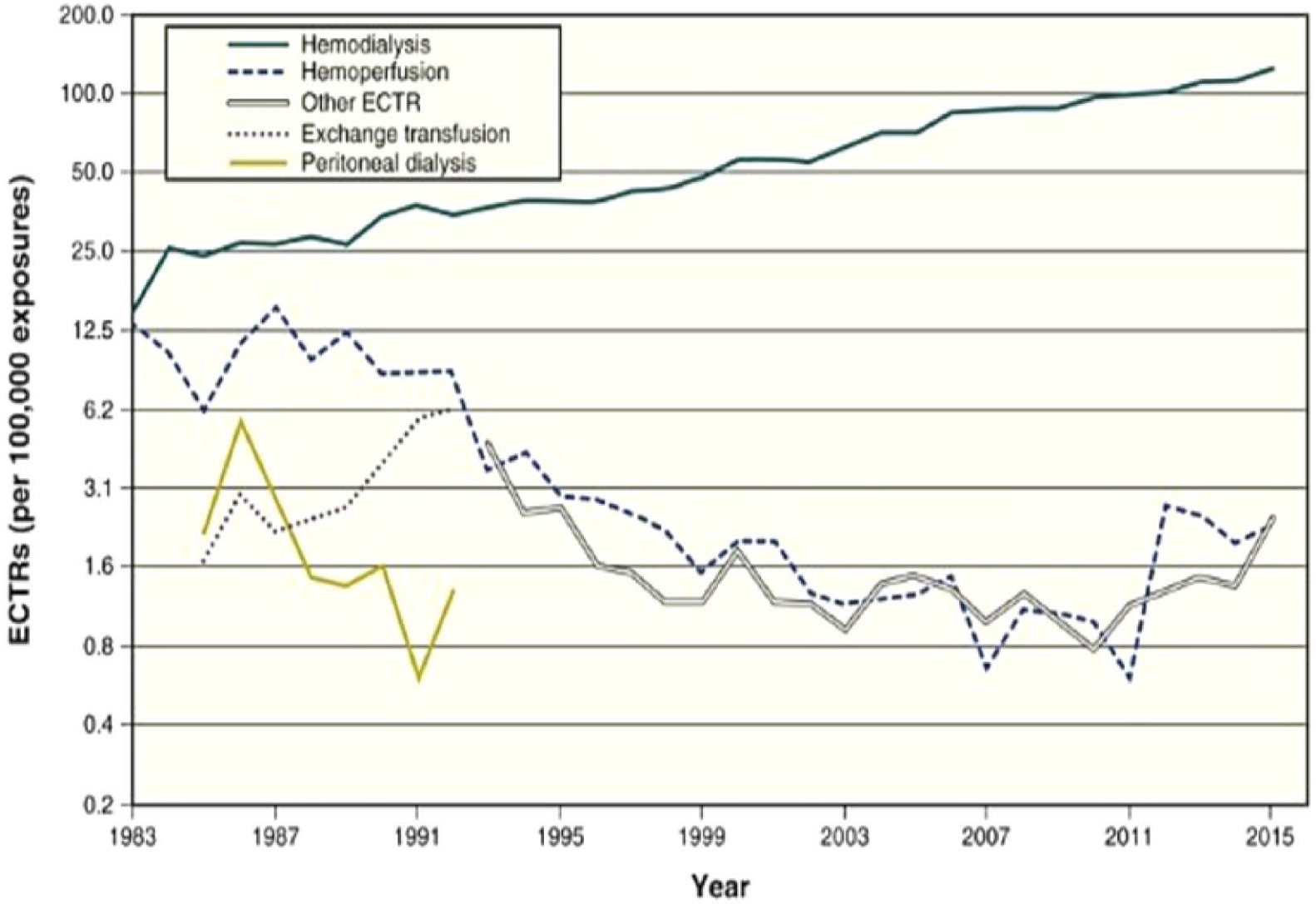


FIG. 67.2 This figure illustrates how often extracorporeal treatments were used in the United States from 1983 to 2015. *ECTR*, Extracorporeal treatment.

HEMODIALYSIS

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

Case history

- A 49 –year-old women was brought to the ED with decrease level of consciousness from two hours before admission. She was treated with metformin 1gr/day due to obesity. She has been taking ibuprofen since last wk due to joint pain. She had nausea ,vomiting and abdominal pain from 2 hours ago, and white tablet have been seen in the contents of the patient's vomit on neurologic exam, she had no focal neurologic sign,pupile was reactive ,midsize . Supportive care (A,B,C,D,E) was done. She was intubated and according to the possibility of drug poisoning ,active charcoal was gavaged (50 gr).

Lab test & vital sign

Vital sign :Bp:90/60, HR:100/min RR:24/min tem:35.5 O2sat:95%.roomair

lab test:

BS:45mg/dl, BUN:25mg/dL ,Cr:1mg/dL ,LFT:normal,

VBG: ph:6.9 ,pco2:24mmhg, po2:70mmhg, Hco3:4.7mEq/l,

Na:142meq/l, K:3.9meq/l, CL:108meq/,Albumine:3.5g/l,

Lactate:23(0.5-2.2),mmol /l

U/A:ketones:negatives

Serum keton:negative

Clinical course

first:

DW50% was immediately infused, but the level of consciousness did not improve.(BS :BS:45mg/dl increased to 180 mg/dl after two vial)

type of acidosis was calculated:

VBG: ph:6.9 ,pco2:24mmhg, po2:70mmhg, Hco3:4.7mEq/l,

Na+k-(CL+HCO3)= AG
AG=30.6 ;Delta Ratio=0.961
Calculated compensation =Expected Pco2 13-17 mmHg
Result:

Metabolic acidosis, elevated anion gap, concomitant respiratory acidosis.

METABOLIC ACIDOSIS
ELEVATED ANION GAP

M: METHANOL, METFORMIN

E: ETHYLENE GLYCOL

T: TOLUENE

A: ALCOHLIC KETOACIDOSIS

L: LACTIC ACIDOSIS

A : ACETAMINOPHEN

C: CO,CYANID,COLCHICINE

I: INH,IRON,IBUPROFEN

D: DKA

G: GENERLIZED SEIZURE DRUGS

A: ASA SALICYLATES

P: PARALDEHYDE, PHENFORMIN

Lactic acidosis

Type A(hypoxic)

- Septic shock
- Hypoperfusion
- Hypoxia
- Hemorrhgic shock
- Regional ischemia

Type B(non-hypoxic)

- Antiretrovirals
- Cyanide
- Salicylate
- Ethanol,alcohols
- Metformin
- Thiamine deficiency
- Bet-adrenergic agonist
- Systemic diseas:malignancy,liver
- D-lactate

Metformin toxicity

Pharmacokinetic of metformine

- Absorption occurs primarily in the upper part of the intestine.
- Excreted, unmetabolized, via transporters in the proximal tubules of the kidneys, and may accumulate in acute and chronic kidney disease.
- The drug has negligible plasma protein binding .
- Vd ranging from 63 to 276 L (1 to 5 L/kg) .
- Elimination half-life of metformin in patients who take multiple doses and have good renal function is approximately five hours .
- endogenous metformin clearance, in the setting of normal kidney function, is 600 ml/min.

Metformin mechanisms of action :

- Reduces the absoption of glucose from intestine.
- Decreases insulin resistance.
- Inhibits gluconeogenesis.
- Increased uptake of glucose by muscle and adipose cell.
- Rarely induce lactic acidosis by partial inhibition of oxidative phosphorylation complex1of the mitochondrial,or through inhibition of pyruvate carboxylase which results in both accelerated lactate production and reduce lactate metabolism.

Metformin toxicity

- Whether the patient has an acute overdose or chronic toxicity, clinicians should also ask whether other antidiabetic agents are used.
- the most common complaints are gastrointestinal, including nausea, vomiting, and diarrhea.
- Alterations in mental status may be due to acidosis or hypoglycemia
- tachycardia, hypotension, and tachypnea in patients with severe lactic acidosis.

Metformin concentration

- unhelpful in most cases , few hospitals perform it.
- rarely available
- does not correlate with the severity of the poisoning or patient outcome
- endogenous metformin clearance, in the setting of normal kidney function, is 600, which far exceeds the clearance achieved by HD (240 ml/min). As such, ECTR is usually not recommended for enhanced elimination in metformin overdose unless there is impaired kidney function.

If undetectable, Nevertheless, it is important to consider other causes of lactic acidosis (eg, sepsis, bowel ischemia) in patients who take metformin

MALA:metformin associated lactic acidosis

- Definition:ph<7.35 and lactate >5 mmol/l , May occur following acute overdose.
- A systematic review of studies involving confirmed acute metformin overdose found that lower serum pH and higher serum lactate concentrations correlated with increased mortality.
- MALA is a serious adverse event with a high mortality rate up to 50%.
- Incidence varies from 0 to 138 per 100,000 patient years .

Sodium bicarbonate

Recommend in severe metabolic acidosis:

- Use in arterial pH < 7.1, or < 7.2 in patients with severe AKI.

- Aim pH > 7.1 , or> 7.3 in patients with severe AKI.
  until the acute toxicity resolves.

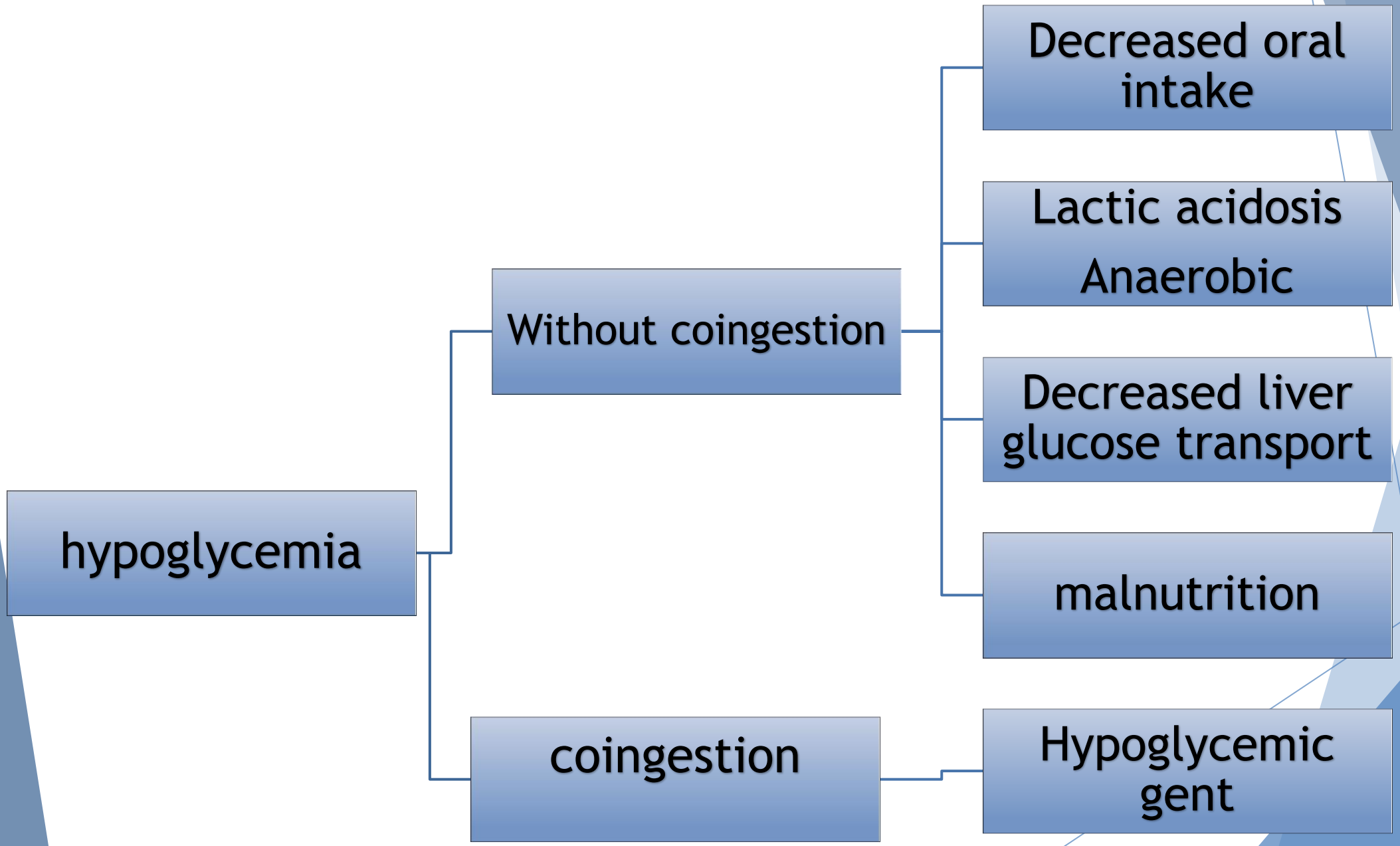
EXTRIP RECOMMENDTION

Indications
➢ ECTR is recommended if: • Lactate concentration greater than 20 mmol/l • Blood pH less than or equal to 7.0 • Standard therapy (supportive measures, bicarbonate, etc.) fails ECTR is suggested if: • Lactate concentration is 15–20 mmol/l • Blood pH 7.0–7.1 Comorbid conditions that lower the threshold for initiating ECTR: • Impaired kidney function • Shock • Decreased level of consciousness • Liver failure

HD IN MALA

- HD is the hemodynamics stable, Continuous hemodialysis (>15 hours) has been used successfully in extremely ill.
- CVVH or CVVHD should be considered in hemodynamically unstable and in metformin overdose .
- CVVH should only be considered in patients who are too hemodynamically unstable .
- Removing metformin.
- Treatment may need to be repeated should metabolic derangements recur.
- Hemodialysis may be discontinued when the lactate concentration is <3 mmol/L and the pH is >7.35

Hypoglycemia and metformin



Nephrologist recommendation:

- 1. Re-administration of bicarbonate and re-check of blood gases
- 2.sepsis must be ruled out, abdominal and pelvic ultrasound were requested at the patient's bedside.
- 3.BOWEL ischemia should be ruled out ,CT angiography requested
- 4.serum level of acetaminophen and salicylate were checked.
- 5. Urgently prepared for hemodialysis.
  Due to the fact that lactic acidosis is resistant to treatment and impaired consciousness in the field of drug use, the ability to dialysis the drug, the patient was catheterized and hemodialysis was performed.