Società Medico Chirurgica di Ferrara

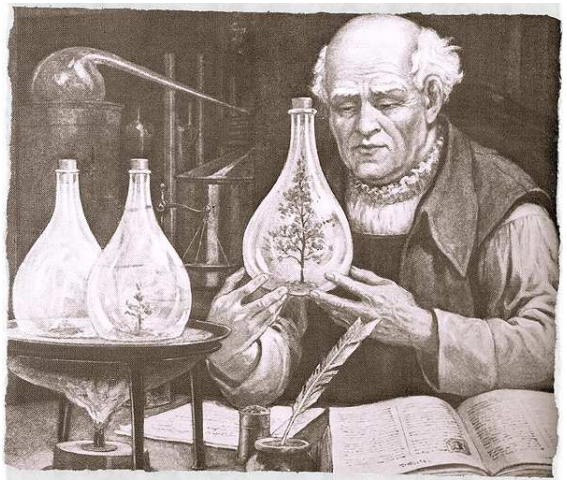

REMDICONTO
DELLE ADUNANZE
dell' Accademia
MEDICO-CHIRURGICA
DI FERRARA
DEGLI ANNI
1846 -- 1847 -- 1848 -- 1849

Terapia sostitutiva extrarenale nel paziente intossicato: indicazioni ed esperienze

Dott.ssa A.Storari

Dott.Y.Battaglia

Sabato 22 ottobre 2016
Aula Magna Nuovo Arcispedale S. Anna
Cona, Ferrara

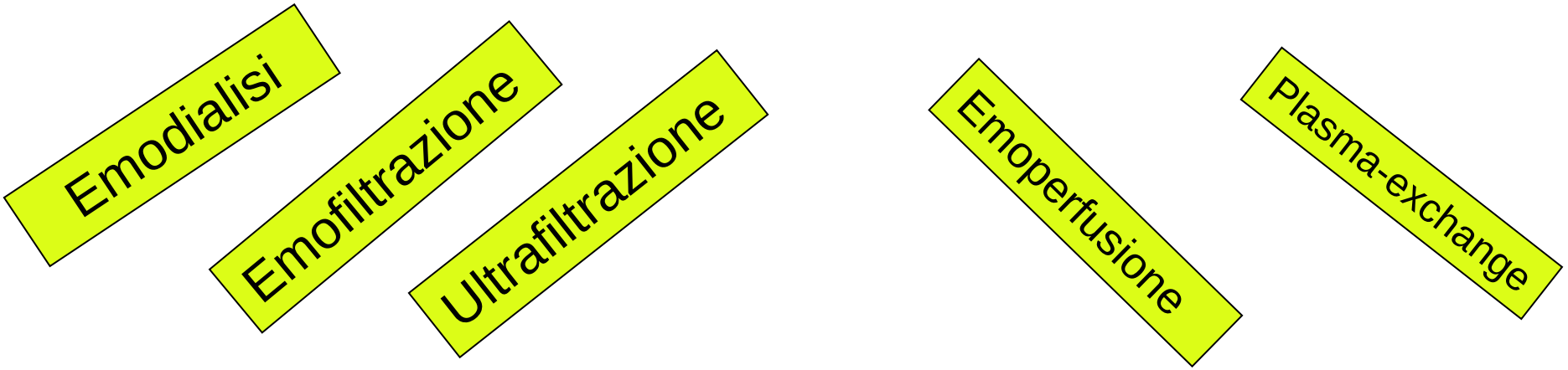


INTERVENTI IN CORSO DI INTOSSICAZIONE

Intossicazione acuta grave consegue all'ingestione del tossico

- Prevenzione o diminuzione dell'assorbimento
- Terapie rianimatorie
- Utilizzo di antidoti
- **Rimozione mediante tecniche di depurazione extracorporee**

Approccio complesso

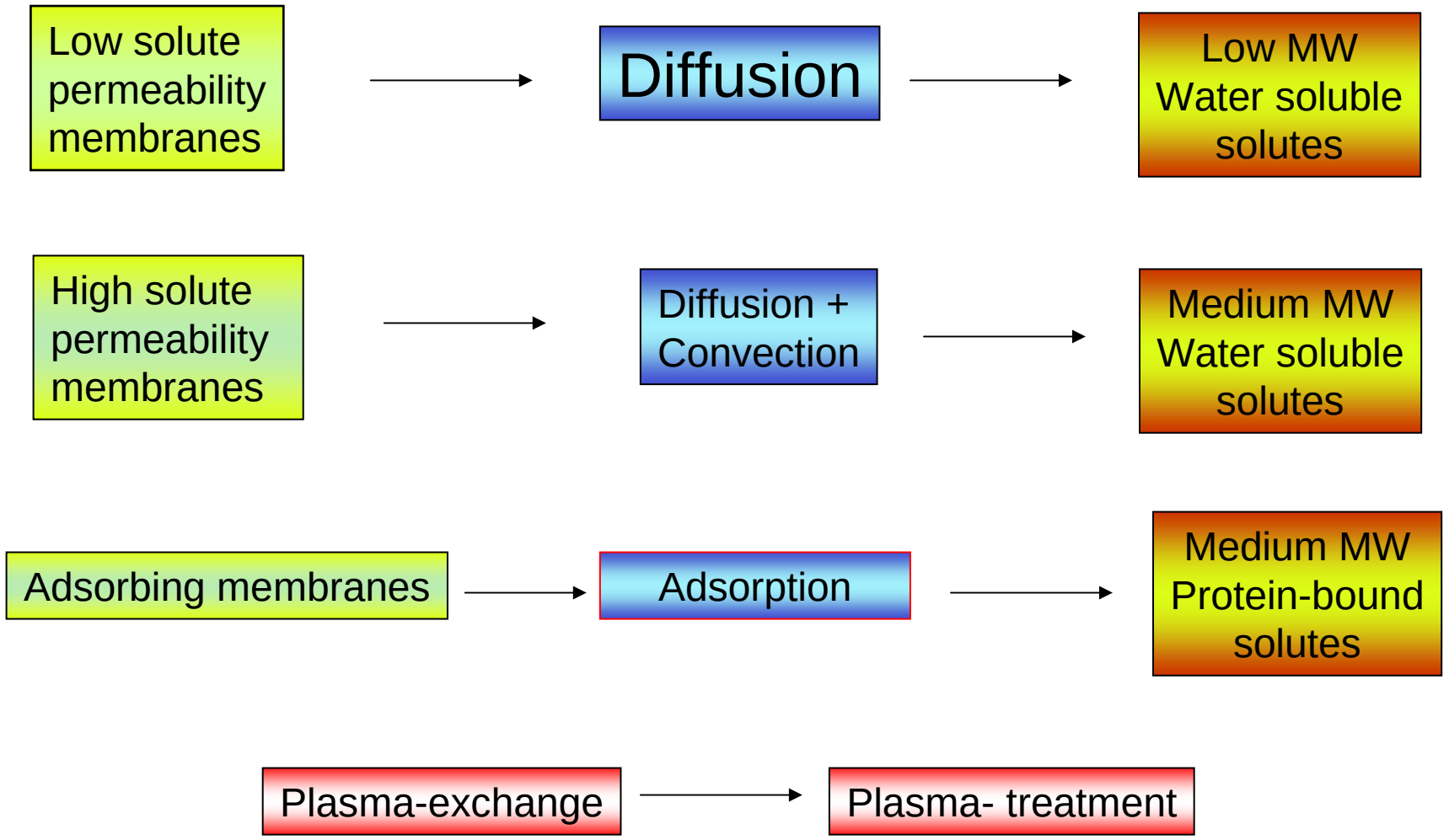


Sistemi ibridi

Intermittente

Continua
CRRT
Continuous Renal Replacement Therapy

THE great steps in (dialysis) blood purification



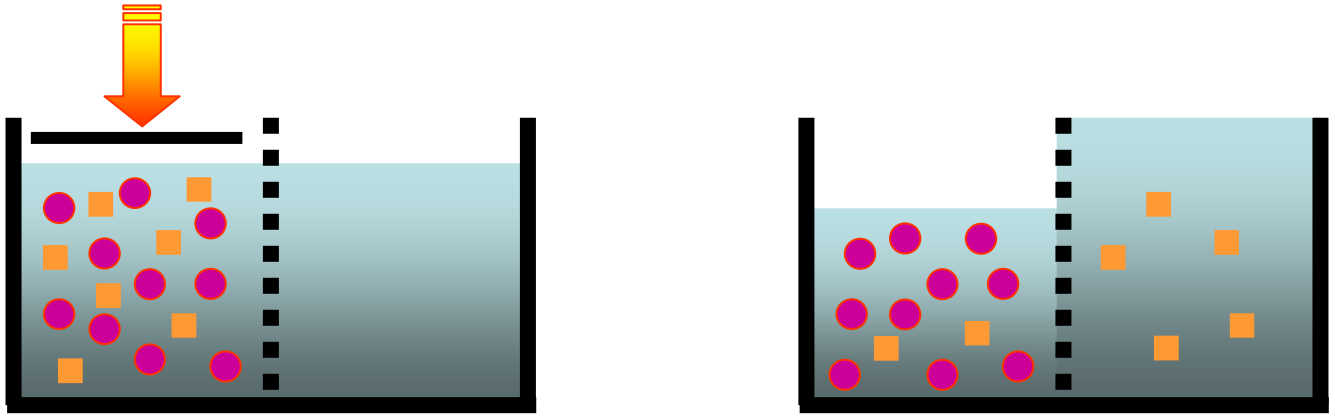
Principi fisici: Diffusione

- Movimento casuale di molecole causato dalla *agitazione termica* che tende a distribuirle in modo uniforme all'interno di una soluzione o fra 2 soluzioni inomogenee separate da una *membrana semipermeabile*

- *Il movimento di soluti avviene senza movimento netto di solvente.*

Principi fisici: Convezione

- Trasporto di soluti per trascinamento da parte del solvente (*solvent drag*) che viene forzato ad attraversare la membrana semipermeabile per effetto di una forza idrostatica (ultrafiltrazione)

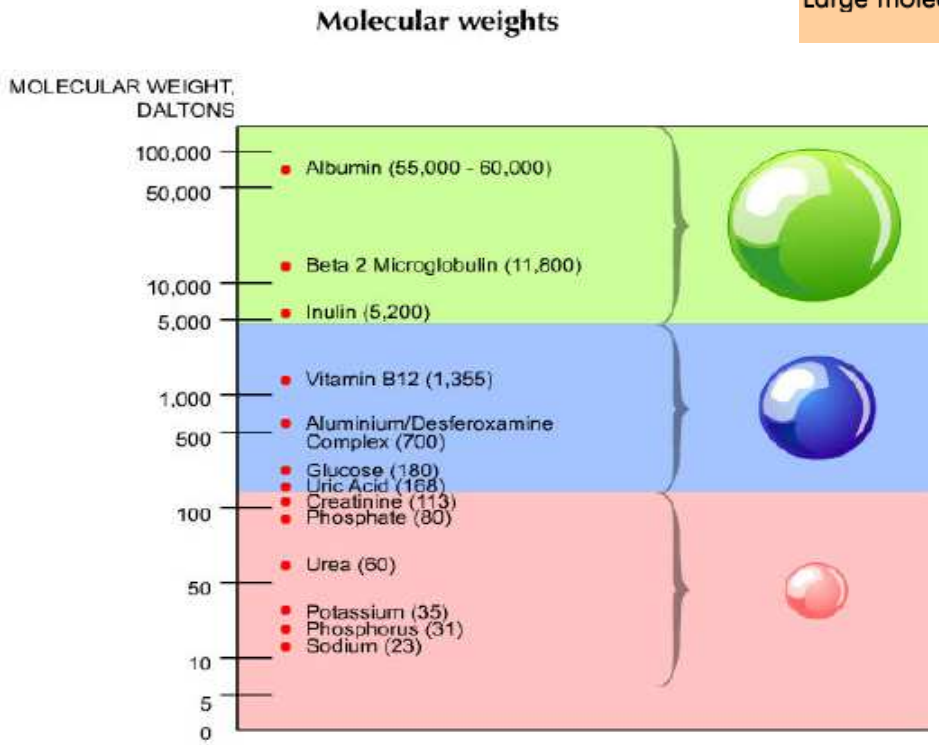


- *Il movimento di soluti avviene con movimento netto di solvente.*

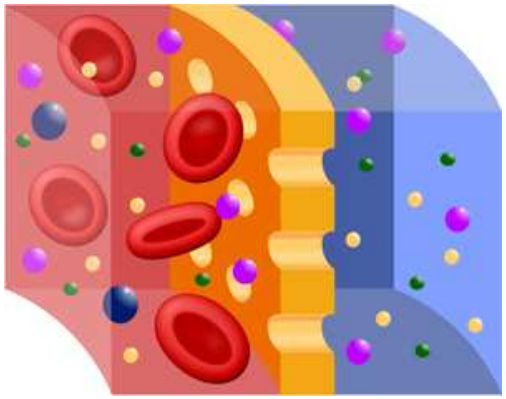
Cinetica di rimozione

- Peso molecolare
- Legame alle proteine

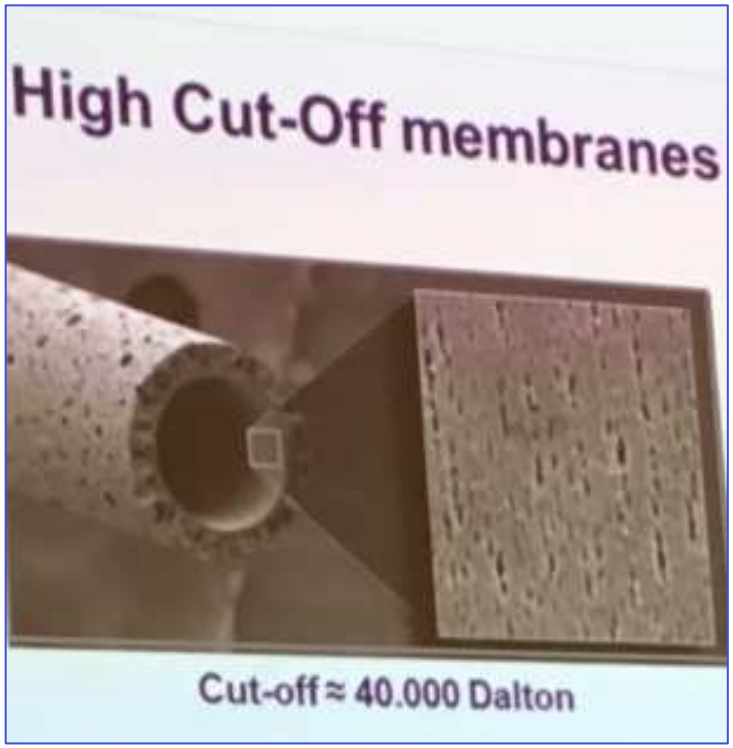
Small molecules	< 300 daltons, e.g., urea, creatinine, Na+
Intermediate molecules	500 - 5,000 daltons, e.g., B12
Large molecules	5,000 - 50,000 daltons, e.g., LMW proteins - beta 2 microglobulins, cytokines, myoglobin

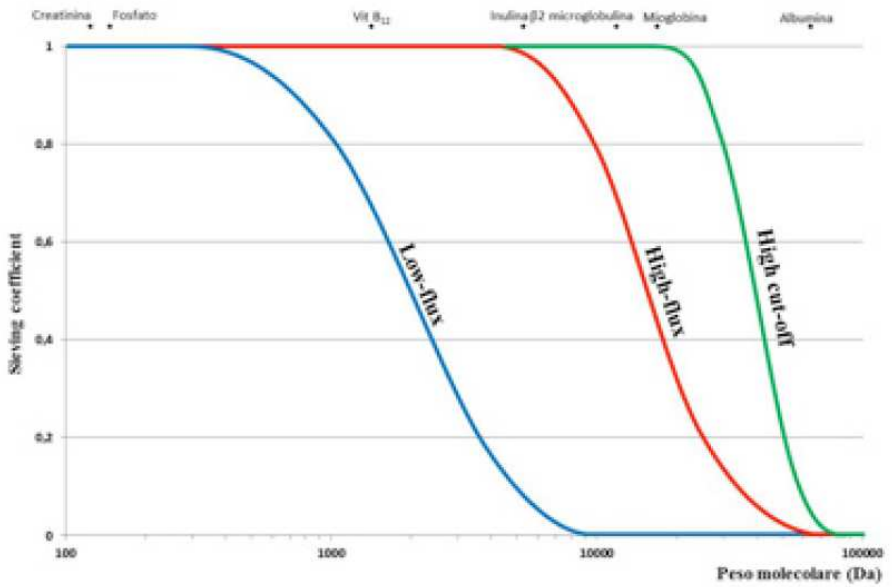


Membrane semipermeabili



- ***Cellulosa***
  - Cellophane
  - Cuprophane
  - Hemophane
- ***Derivati della cellulosa***
  - Acetato di cellulosa,
  - diacetato di cellulosa
  - Triacetato di cellulosa
  - Cuprammonio
- ***Membrane sintetiche:***
  - Idrofile
    - Policarbonato polietere
  - Idrofobe
    - Poliacrinonitrile (nephral ® hospal)
    - Polieteresulfone (BLS ® Sorin)
    - Polifenilsulfone (pureflux ® Nipro)
    - Polisulfone a basso flusso (F ® fresenius)
    - Polisulfone ad alto flusso (HF ® fresenius)
    - Poliarileteresulfone (Arylane ® gambro)
    - Poliamide (polyflux® gambro)
    - Polimetilmetacrilato (filtryzer ® Toray)
    - Helixone (FX ® fresenius)





SC facilità di un soluto da attraversare la membrana

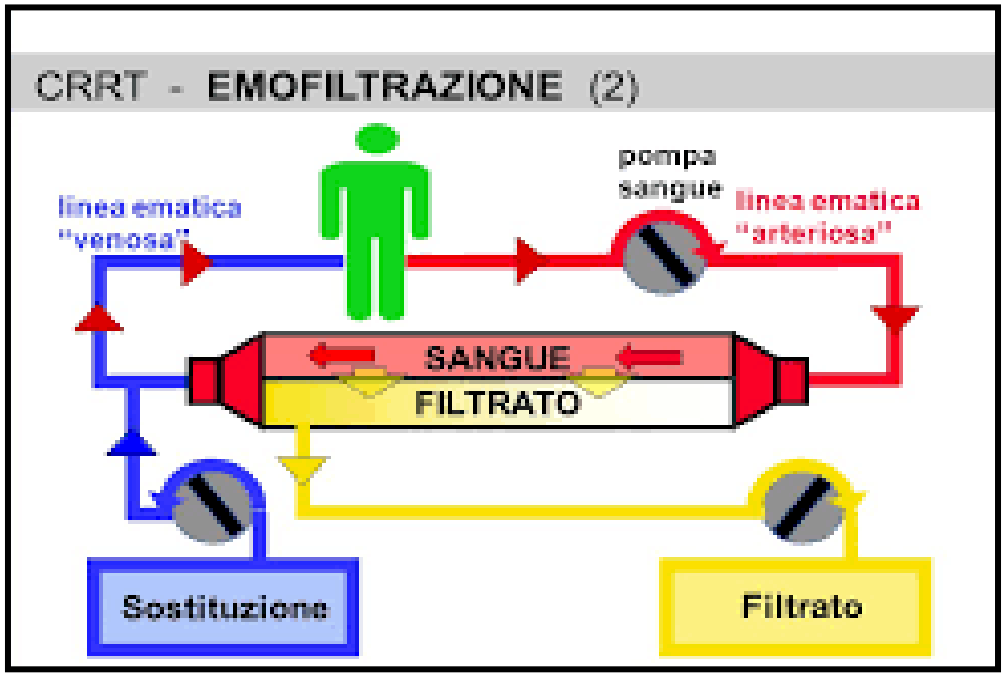
Profilo schematico dei valori di SC di diversi soluti per membrane low-flux, high-flux e high cut-off.

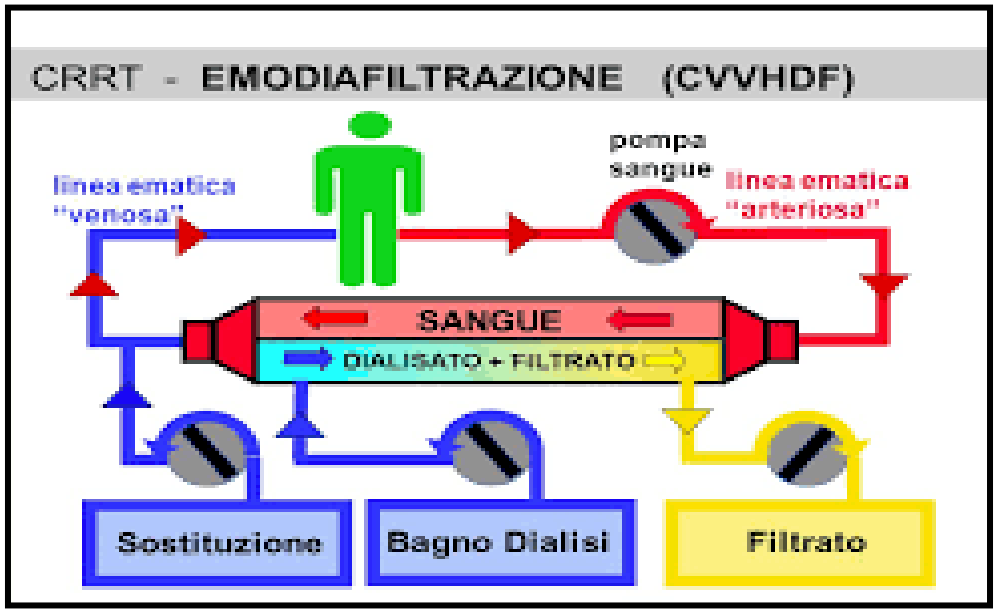
Increase in pore size → Transfer of protein-bound solutes

Transfer of very high MW solutes

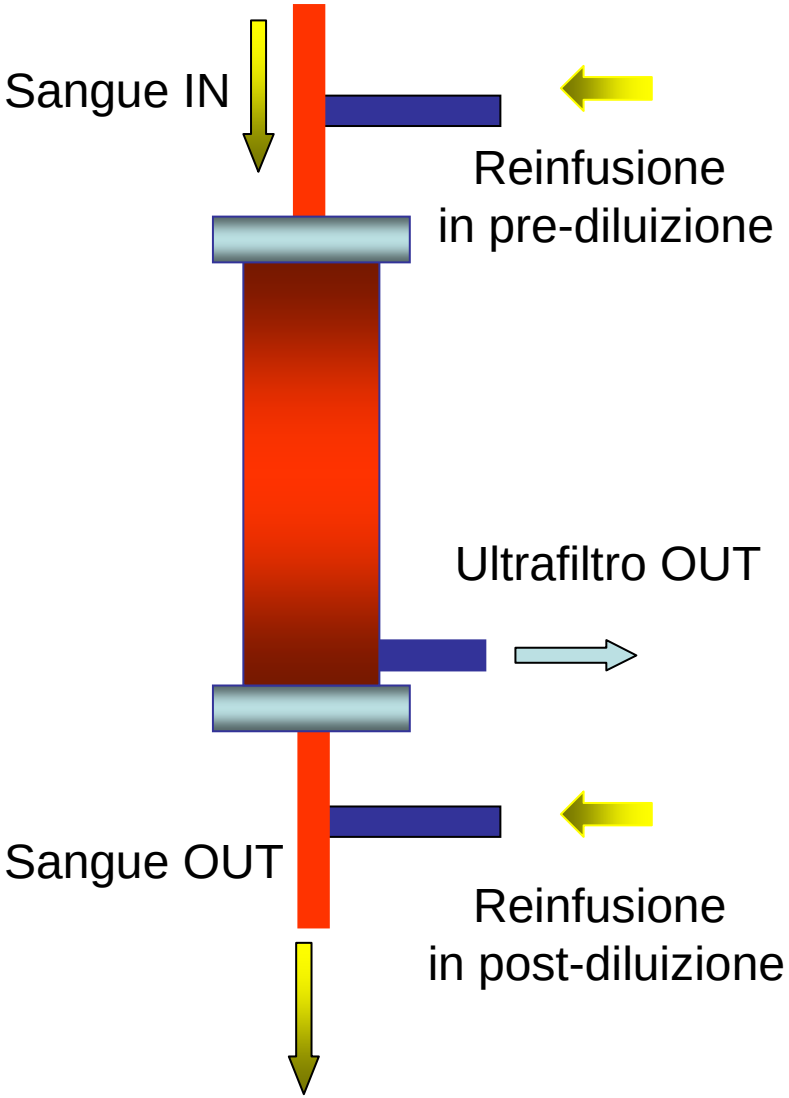
Fattori da considerare nella rimozione del tossico

- **CLEARENCE: valutare se prevalente escrezione del tossico via renale**
- **VOLUME DI DISTRIBUZIONE: se il volume di distribuzione del tossico è elevata (distribuzione multicompartimentale) la rimozione del tossico sarà prolungata**
- **LEGAME PROTEICO: maggiore il legame proteico più difficoltosa la rimozione con RRT**
- **PESO MOLECOLARE: maggiore il peso molecolare, più difficile la rimozione con RRT**


CRRT - EMOFILTRAZIONE (2)
pompa sangue
linea ematica "venosa"
linea ematica "arteriosa"
SANGUE
FILTRATO
Sostituzione
Filtrato


CRRT - EMODIAFILTRAZIONE (CVVHDF)
pompa sangue
linea ematica "venosa"
linea ematica "arteriosa"
SANGUE
DIALISATO + FILTRATO
Sostituzione
Bagno Dialisi
Filtrato

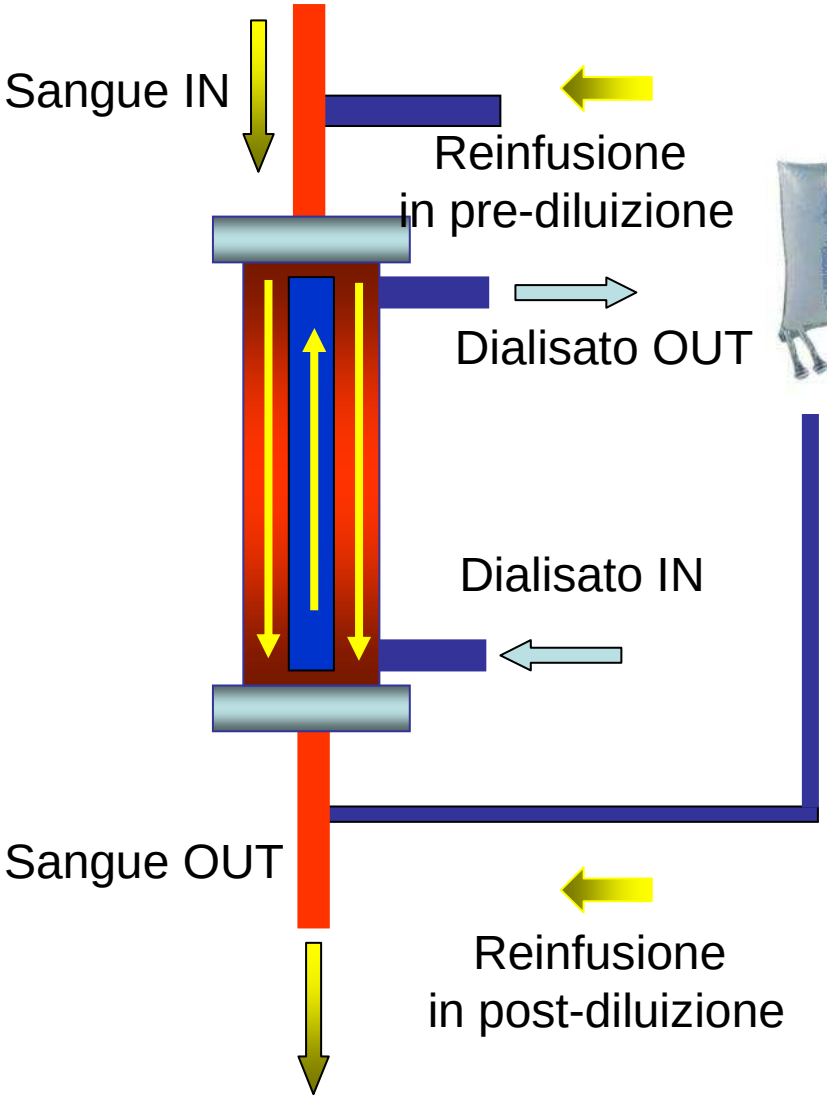
Emofiltrazione CVVH



✓***Membrane ad elevata permeabilità***
✓***Elevato contenuto di liquido di reinfusione***

Rimozione soluti ad elevato PM

Emodiafiltrazione CVVHDF

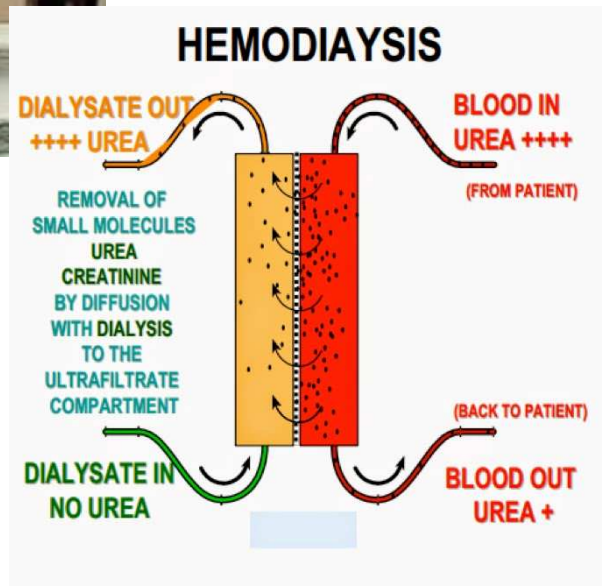


- ✓***Membrane ad elevata permeabilità***
- ✓***Elevato contenuto di liquido di reinfusione***

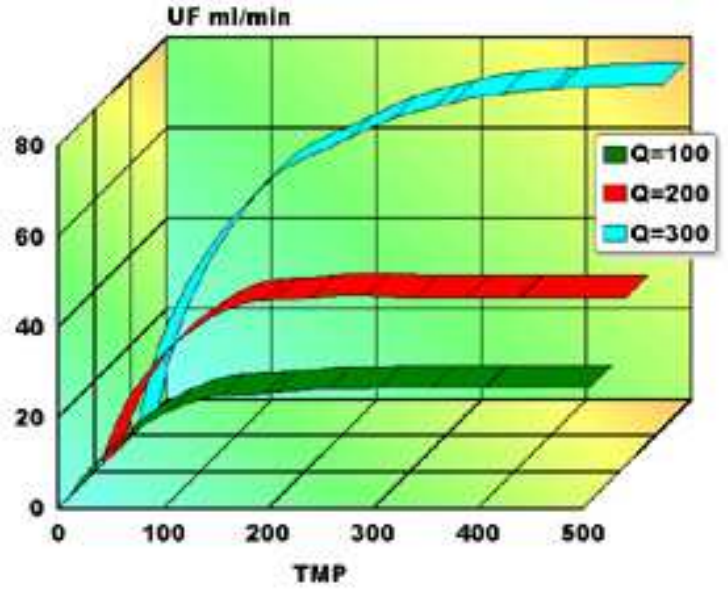
Rimozione sia di piccole che di medie molecole
Migliore efficienza dialitica

Quf = CH2O x S x TMP

C_{H2O} idraulica della membrana **S** superficie della membrana **TMP** pressione transmembrana



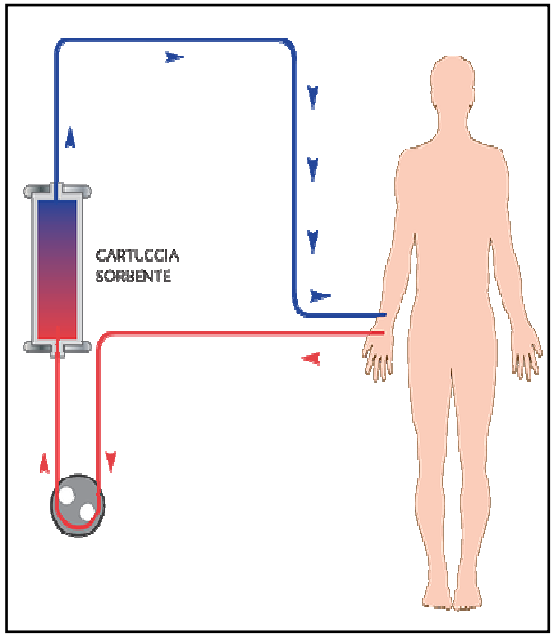
Il flusso ematico (Q) e la TMP influenzano la produzione di ultrafiltrato (UF)



U.S. Food and Drug Administration

Hemoperfusion

Activaded charcoal

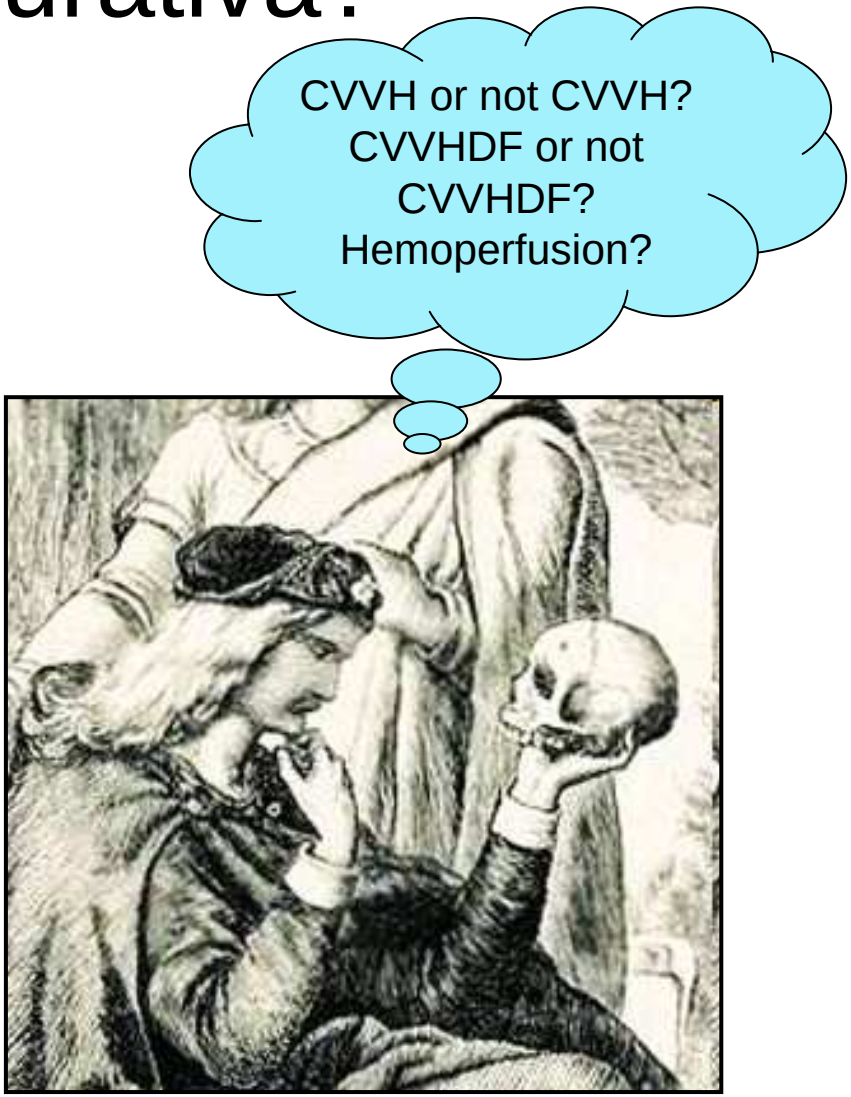


Phenobarbital
Barbiturates
Gluthemide
Theophylline
Digitalis
Hypnotics
Paraquat
Acetaminophen

Normal dialysis machine
2-3 h treatment
Post treatment platelet control
No dialysis,no fluid removal, no acid-base correction ⟶ combine HD

Qual è la migliore tecnica depurativa?

- Metodica?
- Durata?
- Adeguatezza?



… un po’ di storia

http://www.kidney-international.org original article

see commentary on page 1231

Use of hemodialysis and hemoperfusion in poisoned patients

William J. Holubek[1], Robert S. Hoffman[2,3,4], David S. Goldfarb[4,5] and Lewis S. Nelson[2,3,4]

[1]Department of Emergency Medicine, New York Methodist Hospital, New York, New York, USA; [2]New York City Poison Control Center, New York, New York, USA; [3]Department of Emergency Medicine, New York University, New York, New York, USA; [4]School of Medicine, New York University, New York, New York, USA and [5]Nephrology Section, Medical Service, New York Harbor VA Medical Center, New York, New York, USA

- Database istituito dalla American Association of Poison Control Center
- Casi di intossicazione analizzati dal 1985 al 2005

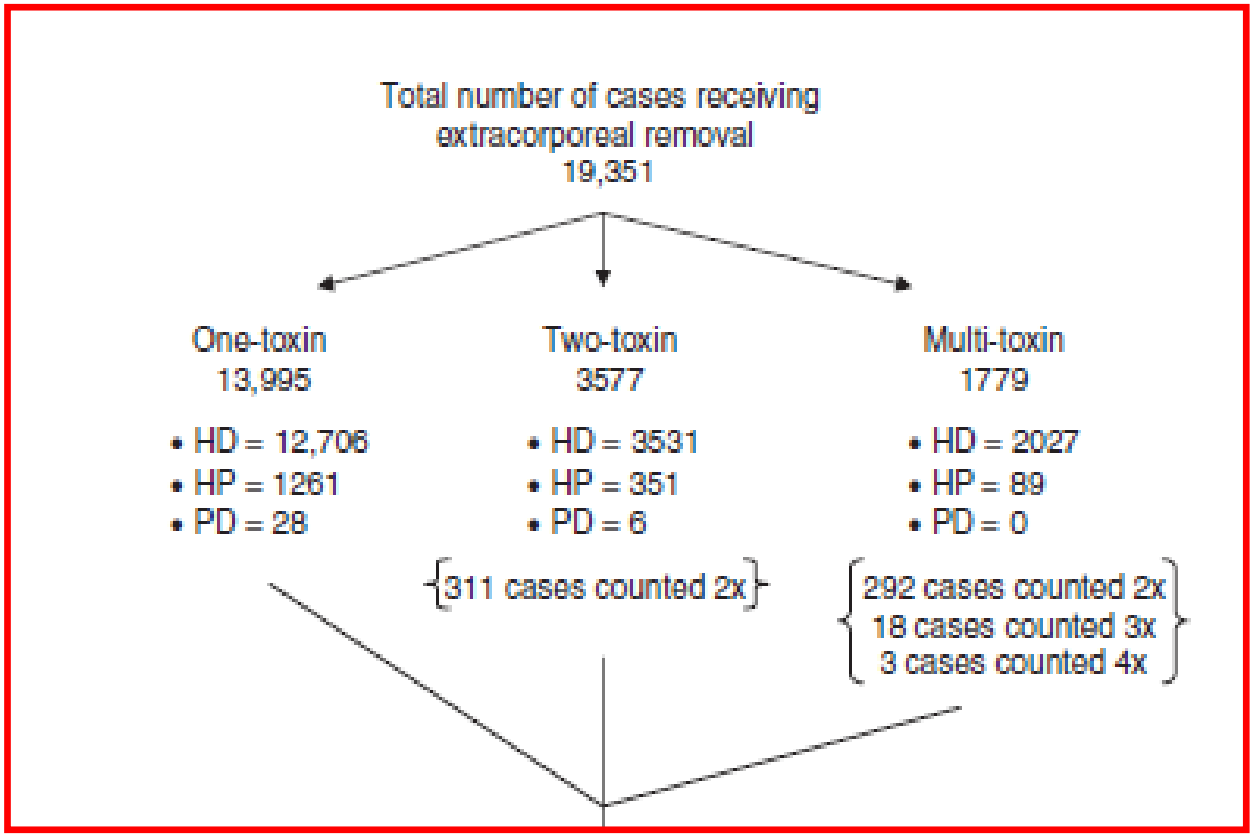


Table 2 | The most common toxins responsible for cases receiving hemodialysis (total number)

1985–1990	1991–1995	1996–2000	2001–2005
Lithium (397)	Lithium (714)	Lithium (1178)	Lithium (2583)
Ethylene glycol (290)	Ethylene glycol (649)	Ethylene glycol (1138)	Ethylene glycol (2077)
Methanol (236)	Salicylates (358)	Salicylates (580)	Salicylates (1490)
Salicylates (233)	Aminophylline (284)	Methanol (289)	Valproic acid (516)
Aminophylline (229)	Methanol (240)	Aminophylline (240)	Acetaminophen (474)
Phenothiazine (73)	Acetaminophen (135)	Acetaminophen (192)	Methanol (463)
Ethanol (73)	Ethanol (84)	Valproic acid (170)	Ethanol (297)
Acetaminophen (71)	Phenothiazine (65)	Ethanol (111)	Benzodiazepine (281)
Isopropanol (49)	Isopropanol (59)	Other (90)	Other (274)

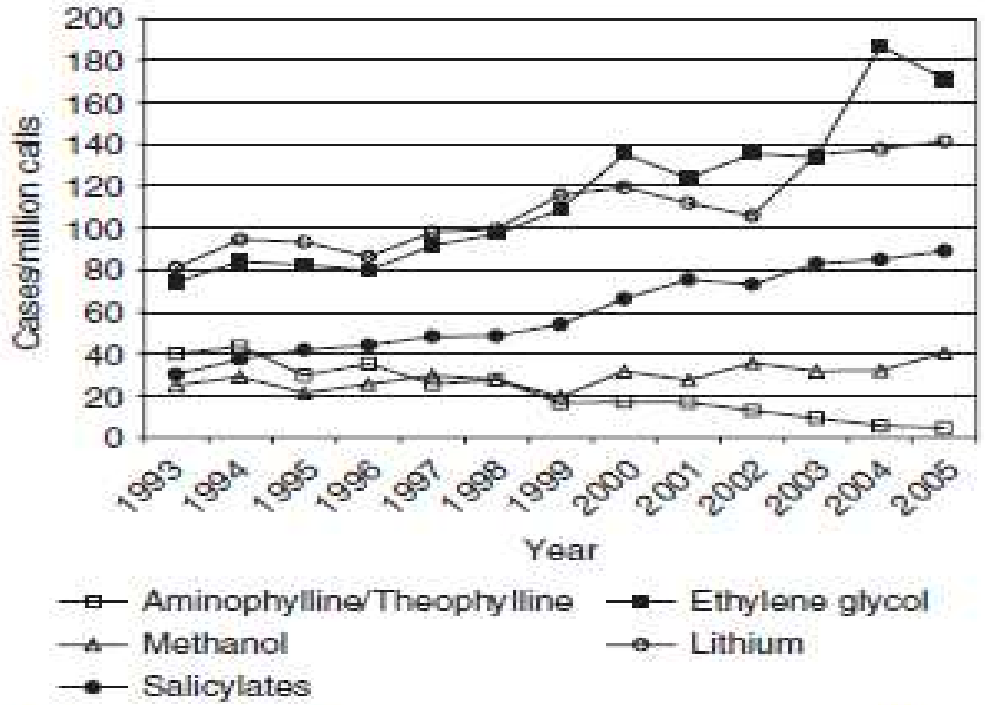


Figure 4 | Trends for the most commonly accepted indication for hemodialysis and/or hemoperfusion.

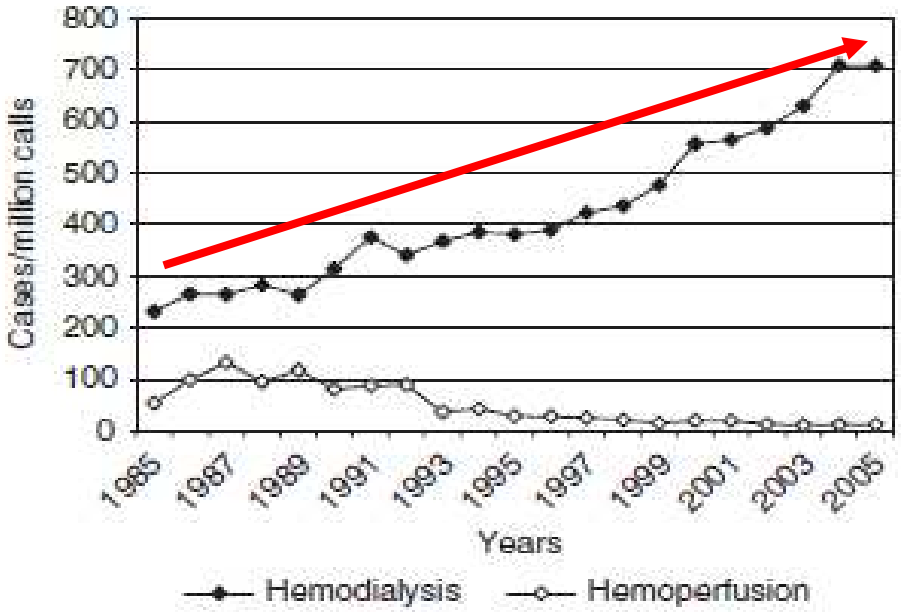


Figure 2 | Normalized number of cases receiving hemodialysis and hemoperfusion.

- Emoperfusione con carbone molto costosa
- Utilizzo di membrane high-flux in HD che rimuovono meglio e più rapidamente il tossico
- Ottima rimozione di molecole ad alto peso molecolare (vancomicina, metotrexate, fenobarbiatle)
- Correzione del metabolismo acido-base

WJ Holubek et al.: Hemodialysis and hemoperfusion in poisoned patients

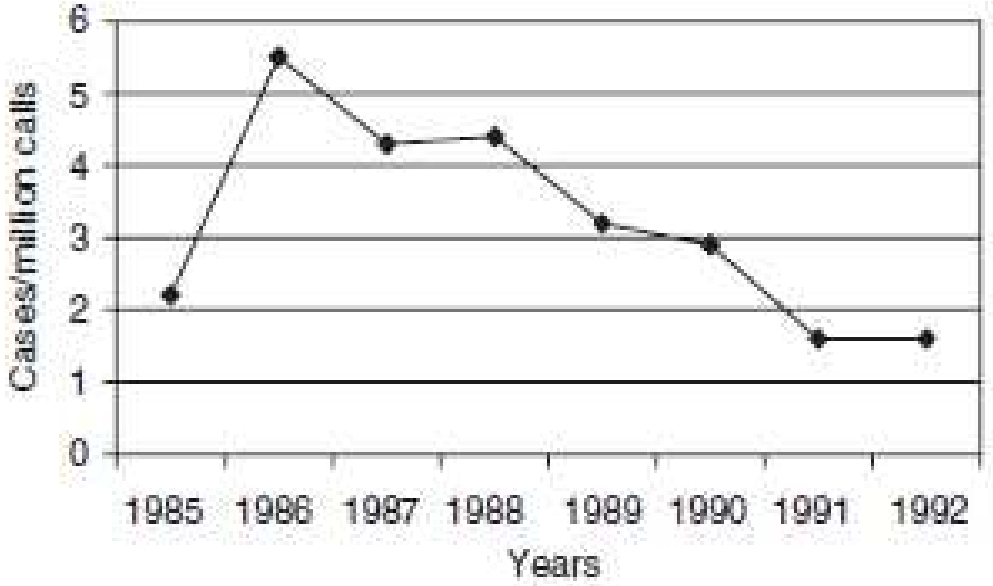


Figure 3 | Normalized number of cases receiving peritoneal dialysis. Peritoneal dialysis was no longer recorded in TESS after 1992.

Il ruolo della dialisi peritoneale è molto limitato per la lentezza della rimozione del tossico con gli scambi peritoneali

The Role of Continuous Renal Replacement Therapy in the Treatment of Poisoning

Jeffrey W. Goodman and David S. Goldfarb

Nephrology Section, New York Harbor VA Medical Center and New York University School of Medicine, New York, New York

Minireview

nephron Clinical Practice

Nephron Clin Pract 2010;115:c1–c6
DOI: 10.1159/000286343

Published online: February 19, 2010

Continuous Renal Replacement Therapy Does Not Have a Clear Role in the Treatment of Poisoning

Zae Kim[a] David S. Goldfarb[b, c]

[a]Division of Nephrology, Nassau University Medical Center, East Meadow, N.Y., and [b]Division of Nephrology, NYU School of Medicine and [c]Nephrology Section, NY Harbor VA Medical Center, New York, N.Y., USA

CRRT è indicata nel trattamento delle intossicazioni

Considerare le caratteristiche farmacoconetiche del tossico

Considerare le caratteristiche emodinamiche del paziente (emodinamica)

Considerare tecniche combinate Emoperfusione/ Emodialisi sequenziali

TOSSICO	PESO MOLECOLARE (Da)	VOLUME DI DISTRIBUZIONE (L/Kg)	LEGAME PROTEICO (%)	METODICA DI RIMOZIONE
VANCOMICINA	1500 (elevato)	0.2-1.25 (elevato)	75 (elevato)	High –flux HD and CRRT
GENTAMICINA	477 (medio)	0.2-0.3 (basso)	0	Standard HD
LITIO	6.9 (basso)	0.6-0.9 (medio)	0	Standard HD o high-flux HD
METFORMINA	166 (basso)	0.5 (moderato)	0	Standard HD o high-flux HD
ASPIRINA	138 (basso)	0.17 (basso)	90 (elevato)	High-flux HD
TEOFILLINA	180 (basso)	0.45-0.7 (medio-elevato)	60 (medio-elevato)	High-flux HD (eventualmente seguita da CRRT)
CARBAMAZEPINA	236 (basso)	0.8-1.8 (elevato)	78 (elevato)	High-flux HD (eventualmente seguita da CRRT)
ACIDO VALPROICO	144 (basso)	0.1-0.2 (basso)	90% (elevato)	High-flux HD (eventualmente seguita da CRRT)
METOTREXATE	454 (medio)	Acuto (0.18 basso) cronico (0.4-0.8 medio)	50% (medio)	High-flux HD

Bunchman, Ferris. Pediatr Nephrol (2015)

Case Report

- A 70-year-old man
- DM type 2
- Hypertension
- Chronic kidney disease stage 3 (creatinine = 1.4 mg/dL;

  eGFR = 59 ml/min)
- Coronary artery disease
- Congestive heart failure
- Peripheral vascular disease

Mujtaba et al. Eur J Drug Metab Pharmacokinet , 2012

Case Report

- **Symptom:** Nausea,Vomiting and anuria.
- **Physical examination:**
- Malnourished
- Tachypneic (30 breaths/min)
- BMI 17 kg/m2
- Afebrile
- BP 157/83 mmHg (no evidence of orthostatic hypotension).
- Dry mucous membranes

Mujtaba et al. Eur J Drug Metab Pharmacokinet , 2012

Case Report

Laboratory tests

BUN 70 mg/dL

Creatinine 9.5 mg/dL

Acute Kidney Injury

pH 7.28

Bicarbonate 12 mEq/L

Anion gap 20 mEq/L

Lactate 9.4 mEq/L

Lactic Acidosis

Mujtaba et al. Eur J Drug Metab Pharmacokinet , 2012

Case Report

- ***Main Medication:***
- Hydrochlorothiazide 25 mg/die
- Furosemide 40 mg/die
- Losartan 50 mg/die
- Glyburide/ Metformin 10/1,000 mg x 2 / die

Mujtaba et al. Eur J Drug Metab Pharmacokinet , 2012

Metformin: GFR

eGFR level (mL/min per 1.73 m^2)	Action
≥60	No renal contraindication to metformin
	Monitor renal function annually
<60 and ≥45	Continue use
	Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution
	Use lower dose (e.g., 50%, or half-maximal dose)
	Closely monitor renal function (every 3 months)
	Do not start new patients on metformin
<30	Stop metformin

Additional caution is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially interacting medications.

ADA Guidelines , 2011

Metformin: Side Effects

System organ class Adverse reaction	Frequency
Metabolism and nutrition disorders	
Lactic acidosis	Very rare
Vitamin B12 deficiency*	Very rare
Nervous system disorders	
Metallic taste	Common
Gastrointestinal disorders	
Gastrointestinal symptoms†	Very common
Hepatobiliary disorders	
Liver function disorders, hepatitis	Very rare
Skin and subcutaneous tissue disorders	
Urticaria, erythema, pruritis	Very rare

Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus

New search | Review | Intervention

Shelley R Salpeter, Elizabeth Greyber, Gary A Pasternak, Edwin E Salpeter (posthumous)

First published: 20 January 2010

……there is **no evidence** that therapeutic doses of metformin are associated with the development of LA…….

……most of the reported cases have occurred in patients with other severe acute conditions, which could have been the real cause of LA……..

BUT

…..patients with renal failure was listed as an exclusion criterion in most of the included studies…….

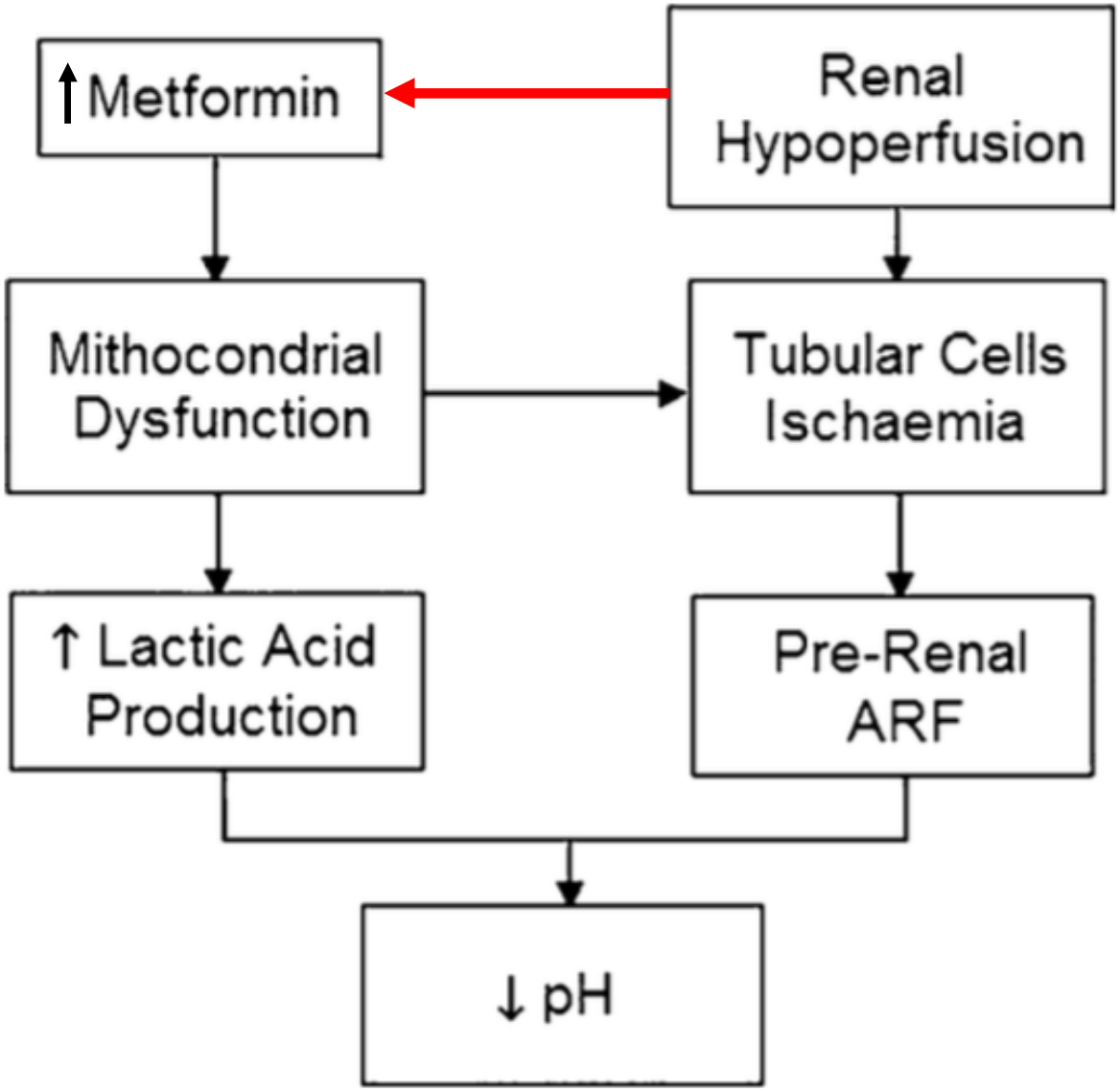
MALA
Metformin-Associated Lactic Acidosis

1 to 30 cases per 100,000 patient-years

Type A (anaerobic)		Type B (aerobic)	
Shock –	Cardiogenic	Systemic disease	Diabetes
	Endotoxic (septic)		Neoplasia
	Hypovalaemic		Hepatic failure
			Renal failure
Heart failure		Drugs	Biguanides
Asphyxia			Ethanol/methanol
Carbon monoxide poisoning			Salicylate overdose
			Inborn errors of metabolism

Donnelly al. Handbook of Diabetes 2014

MALA: Hypothesis



Cucchiari et al. Acta Diabetol, 2016

MALA: Diagnosis

- **ph < 7,35**
- **Lactate > 5 mmol/l**
- **Anion Gap elevato: Na – [HCO3 + Cl] >12**
- **Metformin plasma levels?**

Fitzgerald E et al. BMJ 2009

Case Report

- pH 7.28
- Bicarbonate 12 mEq/L
- Anion gap 20 mEq/L
- Lactate 9.4 mEq/L
- Metformin 22 mcg/ml

Mujtaba et al. Eur J Drug Metab Pharmacokinet , 2012

MALA: Therapy

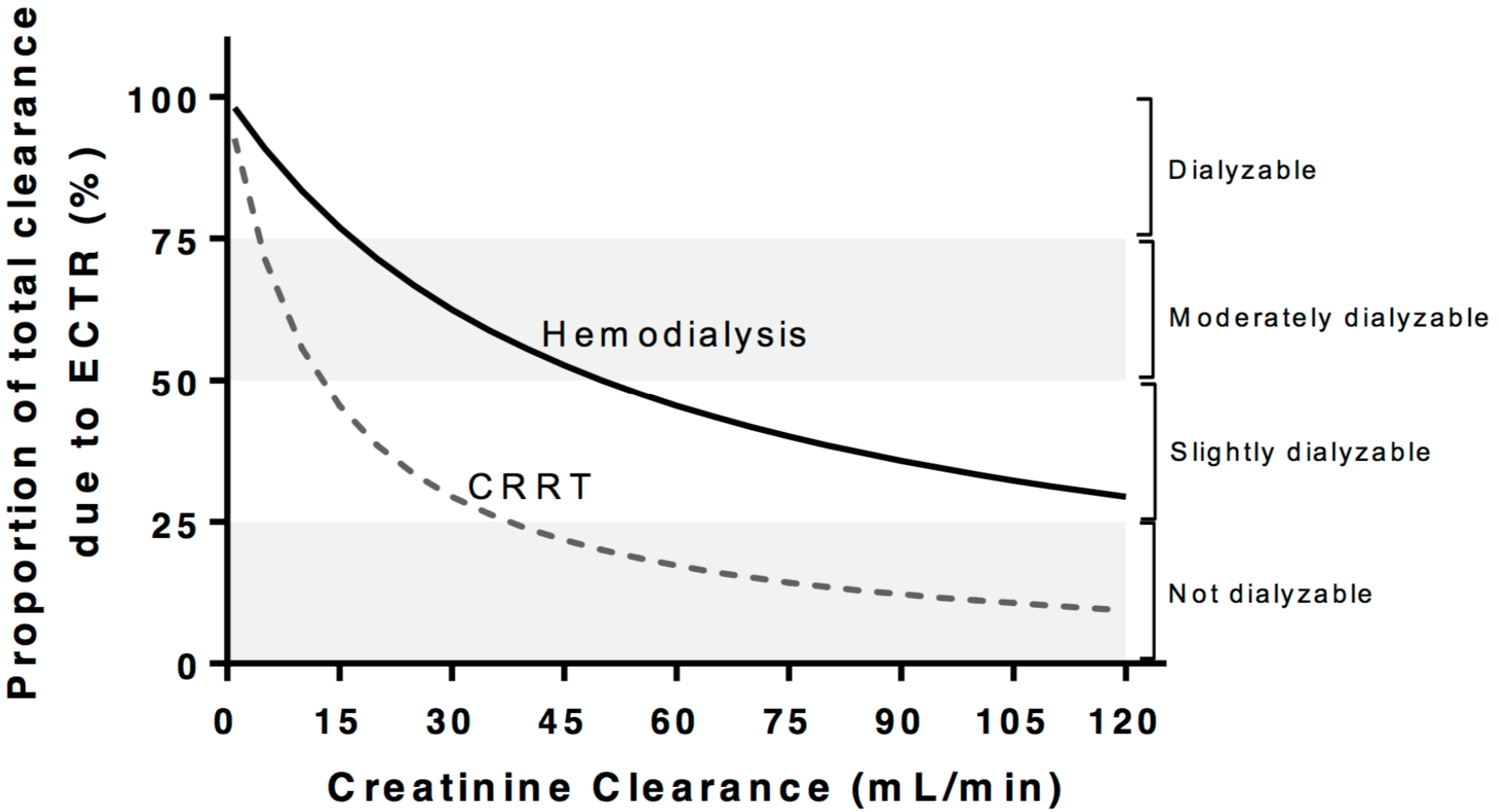
http://www.kidney-international.org the renal consult

When a friend can become an enemy! Recognition and management of metformin-associated lactic acidosis

M Prikis[1], EL Mesler[2], VL Hood[1] and WJ Weise[1]

- Normalize the acid-base imbalance
- Eliminate offending medication
- Treat concomitant disease

Metformin: Grading of Dialyzability



Calello et al. Crit Care, 2015

Extracorporeal Treatments : Indications

ECTR is recommended if

Lactate concentration > 20 mmol/L (180 mg/dL) (1D)

Blood pH ≤ 7.0 (1D)

Standard therapy (supportive measures, bicarbonate, etc.) fails (1D)

Cessation of ECTR is indicated when

Lactate concentration is < 3 mmol/L (27 mg/dL) and pH > 7.35 (1D)

Calello et al. Crit Care, 2015

Extracorporeal Treatments : Indications

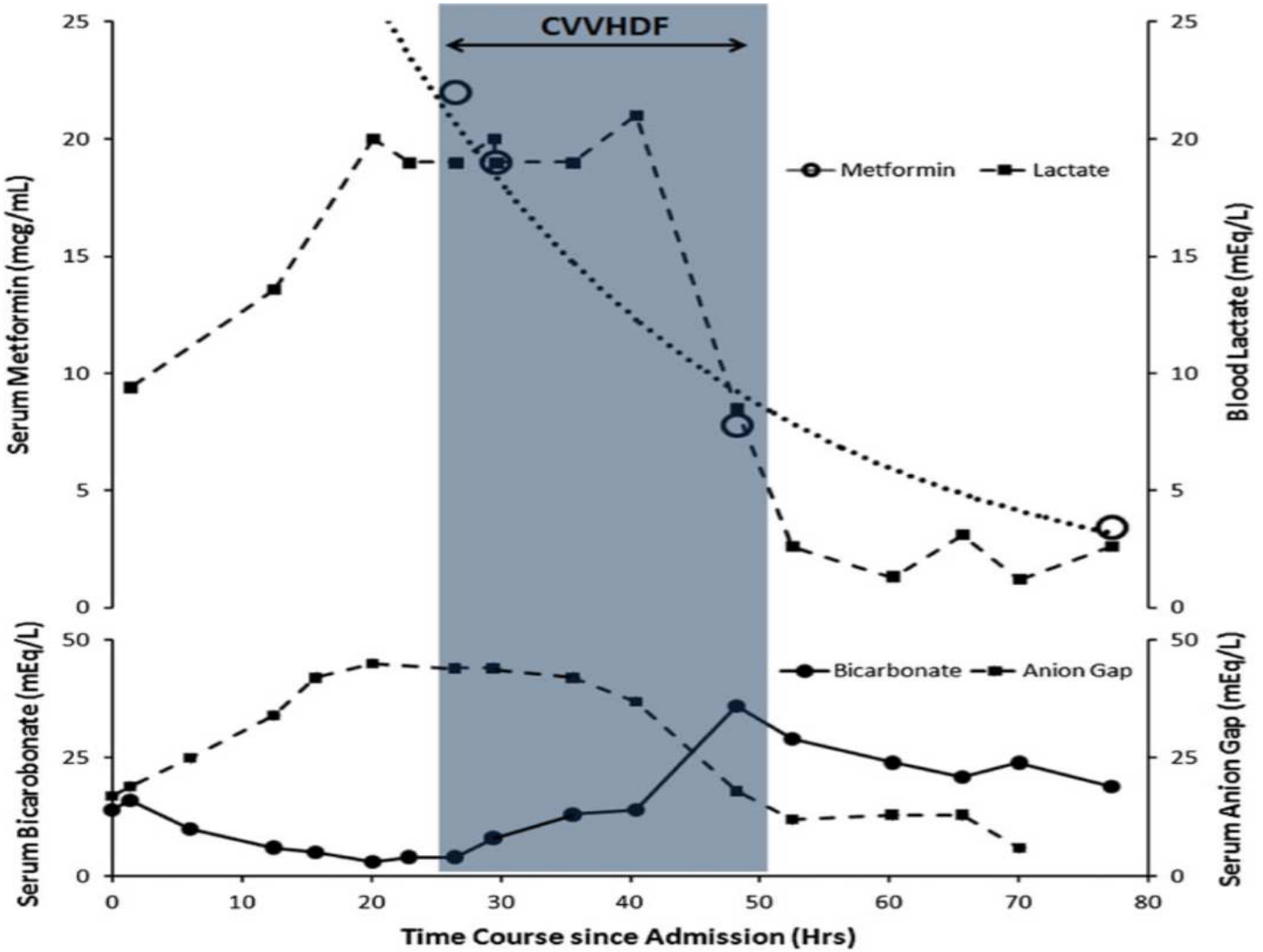
ECTR is suggested if

- Lactate concentration is 15–20 mmol/L (135–180 mg/dL) (2D)
- Blood pH 7.0–7.1 (2D)

Comorbid conditions that lower the threshold for initiating ECTR

- Impaired kidney function (1D)
- Shock (1D)
- Decreased level of consciousness (2D)
- Liver failure (2D)

Calello et al. Crit Care, 2015



Mujtaba et al. Eur J Drug Metab Pharmacokinet , 2012

Case Report

Time	Metformin (µg/mL)	Lactate (mEq/L)	pH	Bicarbonate (mEq/L)	Anion gap (mEq/L)	BUN (mg/dL)	Creatinine (mg/dL)
T1	22	19	7.17	4	44	85	10.7
T2	19	19	7.32	12	44	70	8.6
T3	7.8	7.7	7.71	36	18	30	4.2
T4	3.4	1.2	7.48	19	6	23	3.6

- Resolution of the lactic acidosis
- Started to urinate with Creatinine: 2.6 mg/dL
- CRRT was dicontinued

Mujtaba et al. Eur J Drug Metab Pharmacokinet , 2012

Grazie per l’attenzione