Technical aspects of RRT in AKI: access, anticoagulation, drug dosage and nutrition

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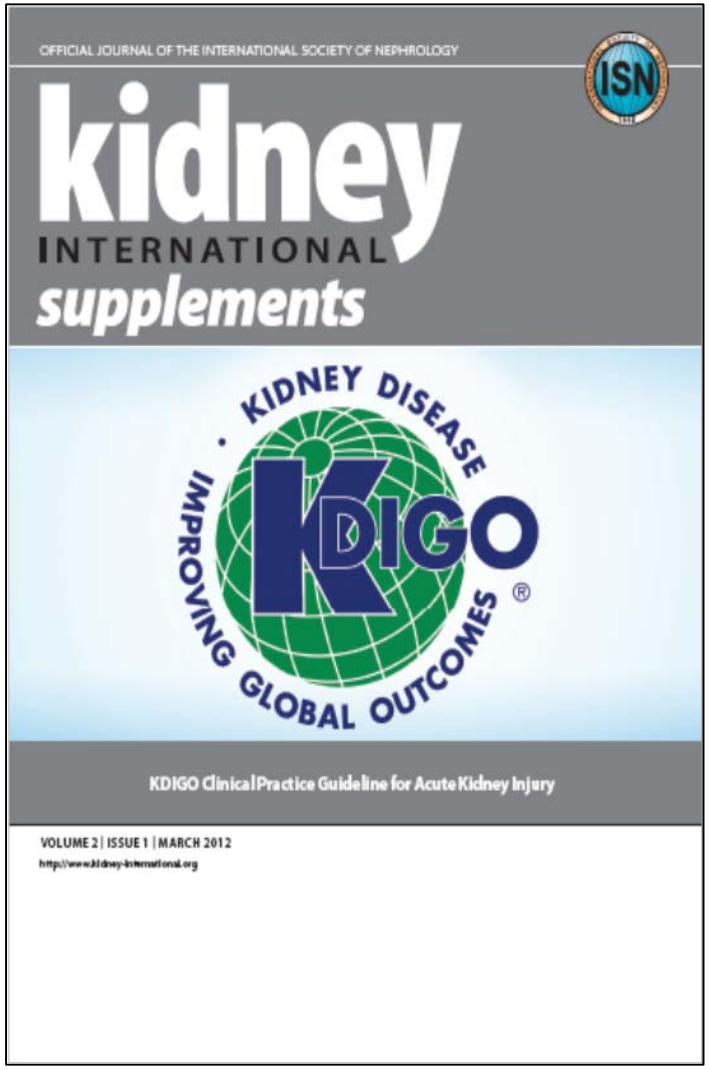
KING'S HEALTH PARTNERS

AKI guideline



March 2012

Chapter 3:
Nutrition

Chapter 5.3:
Anticoagulation

Chapter 5.4:
Vascular access for RRT in AKI

Kidney International 2012; Vol 2: 1 - 141

Vascular access

Vascular access

5.4.1: We suggest initiating RRT in patients with AKI via an uncuffed nontunneled dialysis catheter, rather than a tunneled catheter. (2D)

5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences (Not Graded):

- 1st choice: right jugular vein
- 2nd choice: femoral vein
- 3rd choice: left jugular vein
- Last choice: subclavian vein

Individual patient characteristics may require deviations from this order of preferences.

Vascular access

5.4.5: We suggest not using topical antibiotics over the skin insertion site of a nontunneled dialysis catheter in ICU patients with AKI requiring RRT. (2C)

5.4.6: We suggest not using antibiotic locks for prevention of catheter-related infections of nontunneled dialysis catheters in AKI requiring RRT. (2C)

No comment about duration / line changes

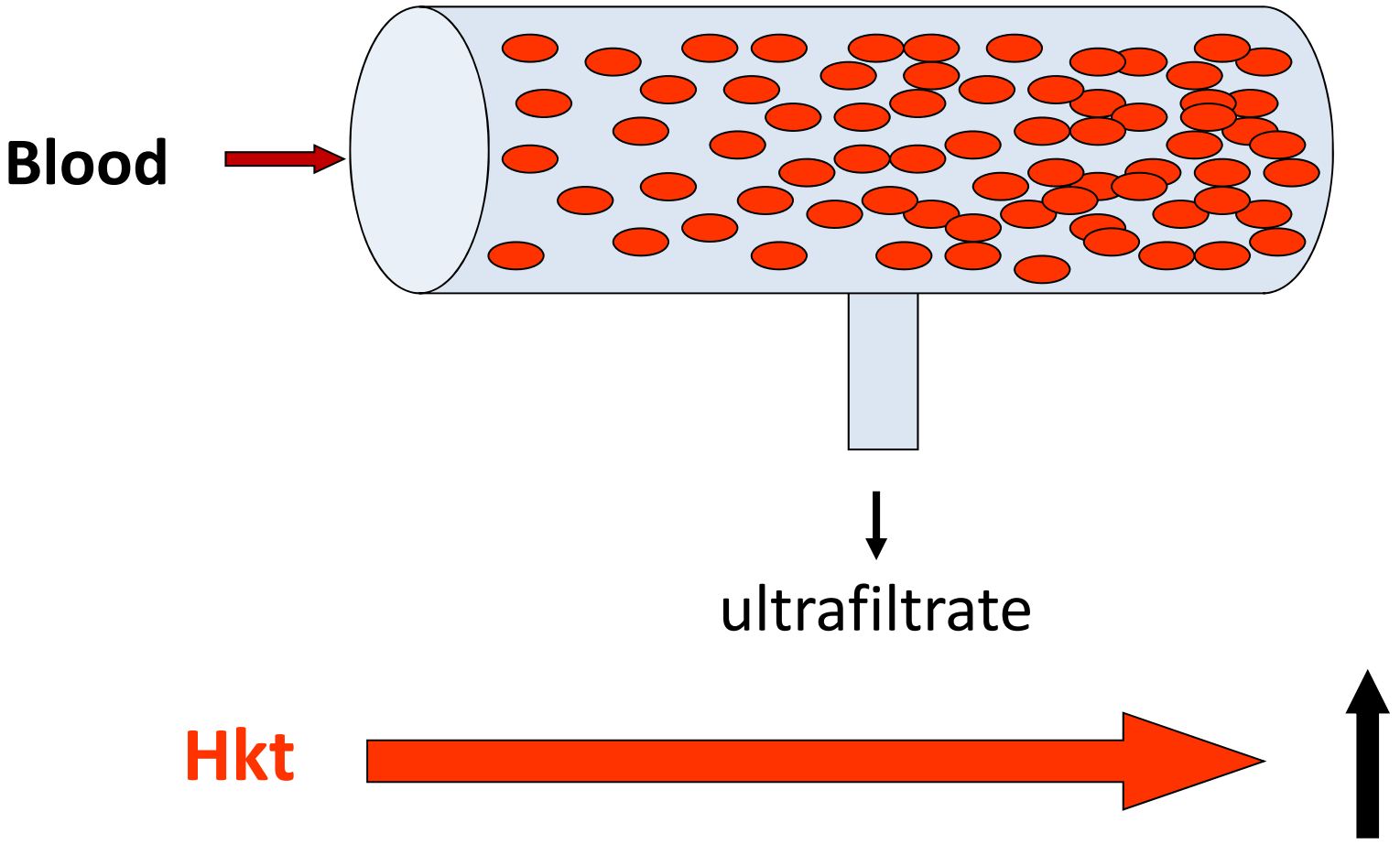
Anticoagulation

Anticoagulation

Hollow fibres providing surface area 0.8 – 2.1 m^2

Circuit clotting

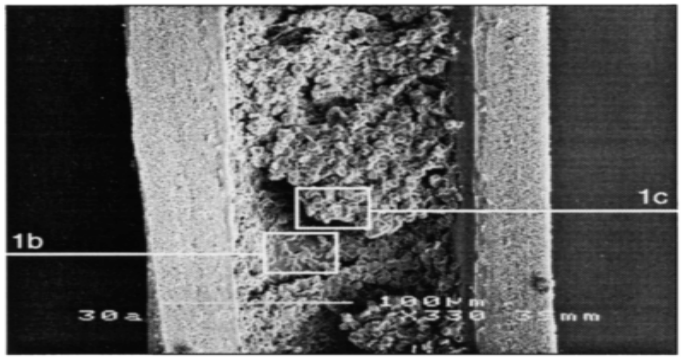
Filter clotting



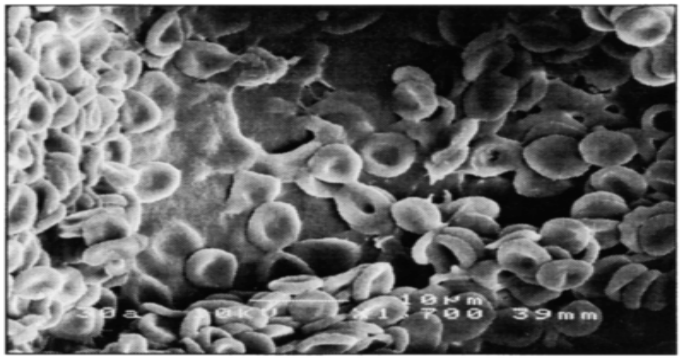
Circuit clotting

1. Haemoconcentration
2. Thrombogenic circuit surface
   (coating of surface with plasma proteins → platelet aggregation)
3. Exposure of blood to air (ie. in drip chamber)
4. Risk factors:
   - low blood flow
   - high Hkt
   - hypercoagulable states
   - filters with large surface area
   - imperfect priming of filter
   - frequent interruption of blood flow
   - lipid infusions (incl propofol)

Circuit clotting



1a



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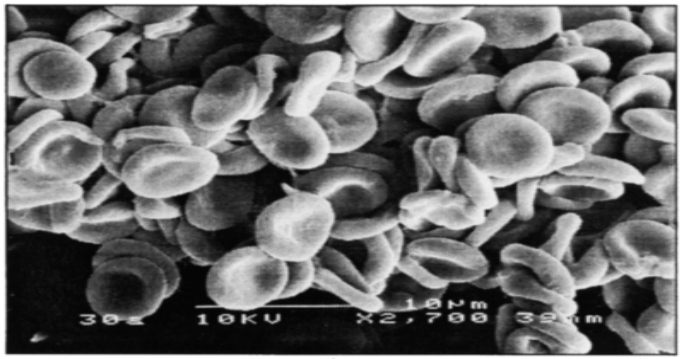


1c

Inner surface of dialyzer membrane during hemodialysis therapy:

dense fibrin network with large amounts of aggregated erythrocytes despite heparin

Hofbauer R et al, KI 1999;56,1578–1583

Anticoagulation

- **Heparin**
- **Prostacyclin**
- **No anticoagulation / regular saline flushes**
- **Regional anticoagulation:**
  with citrate
  with heparin / protamine

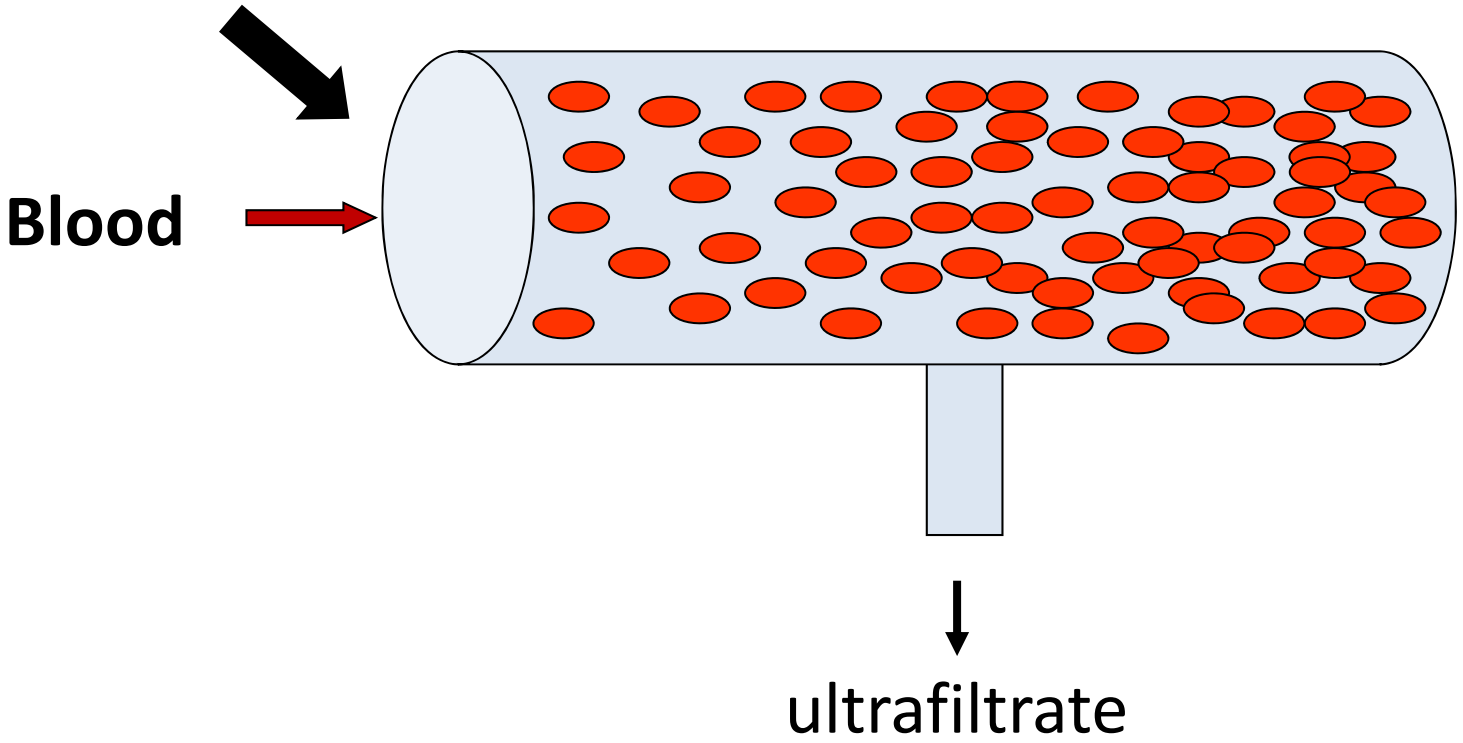
Prevention of circuit clotting without heparin

1. **No anticoagulation**

   flushes with 50-100 mls NaCl 0.9% into prefilter port every 15-30 mins

Prevention of circuit clotting without heparin

Saline flushes
at regular intervals



Prevention of circuit clotting without heparin

1. No anticoagulation

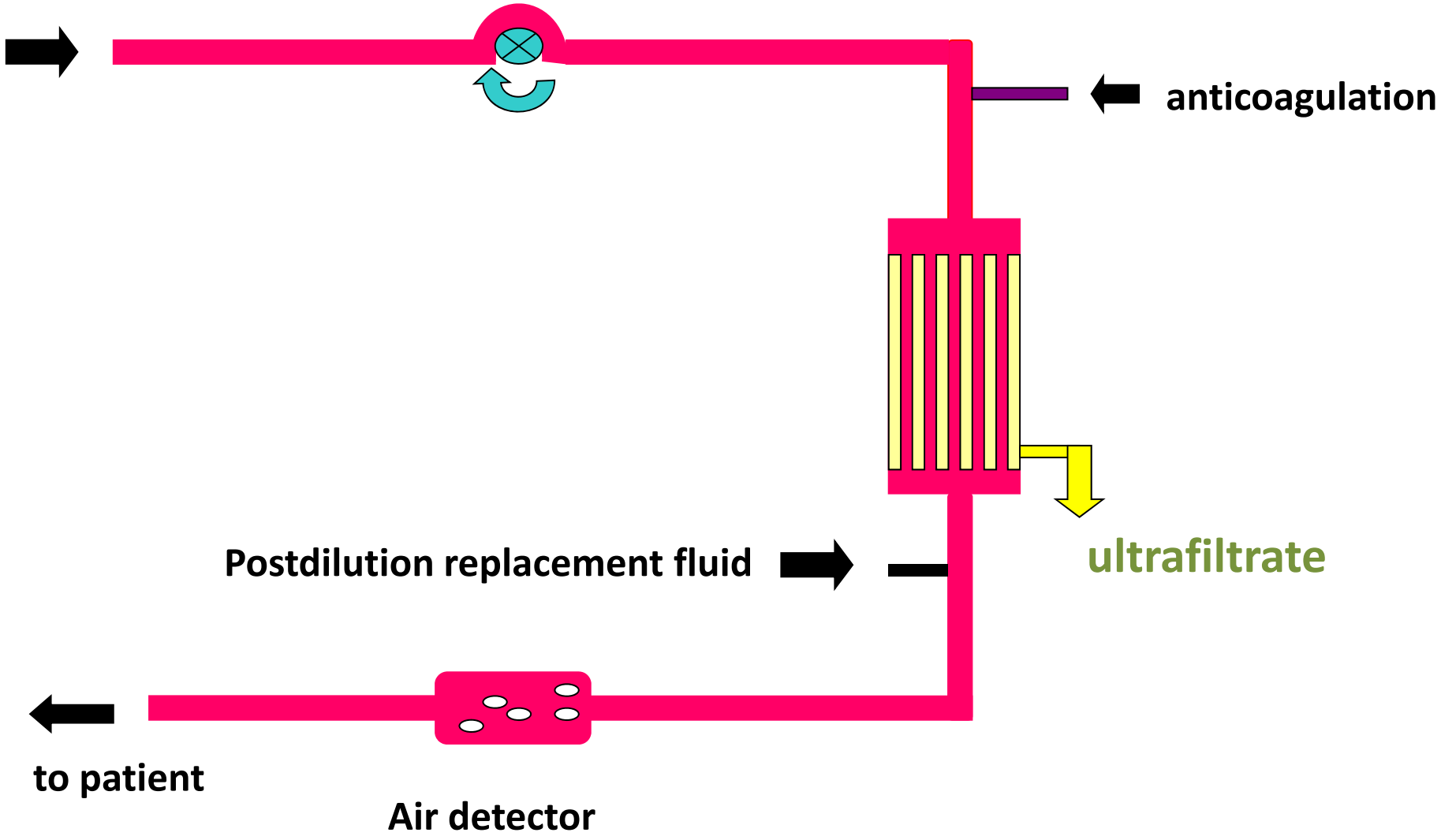
flushes with 50-100 mls NaCl 0.9% into prefilter port

Problems:
nursing workload
need to incorporate boluses into fluid balance

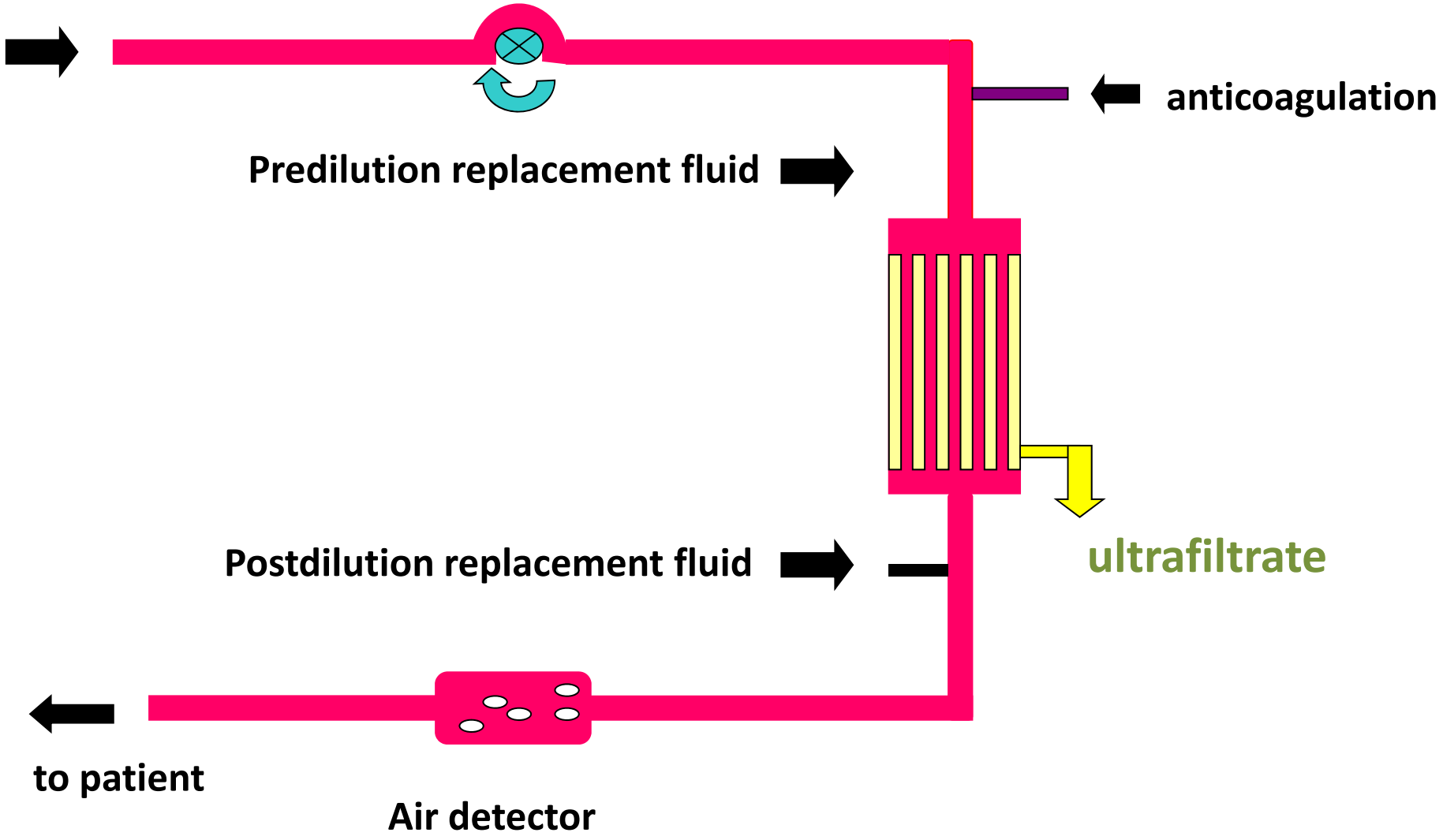
Additional tricks:

increase blood flow rate
change from post-dilution to pre-dilution (but ↑ costs)

Haemofiltration



Haemofiltration



Prevention of circuit clotting without heparin

2. Prostacyclin

inhibitor of platelet aggregation
weaker anticoagulant than heparin
vasodilation
expensive

Prevention of circuit clotting without heparin

3. Regional anticoagulation

Heparin / Protamine combination

Complex
risk of rebound anticoagulation
side effects of protamine

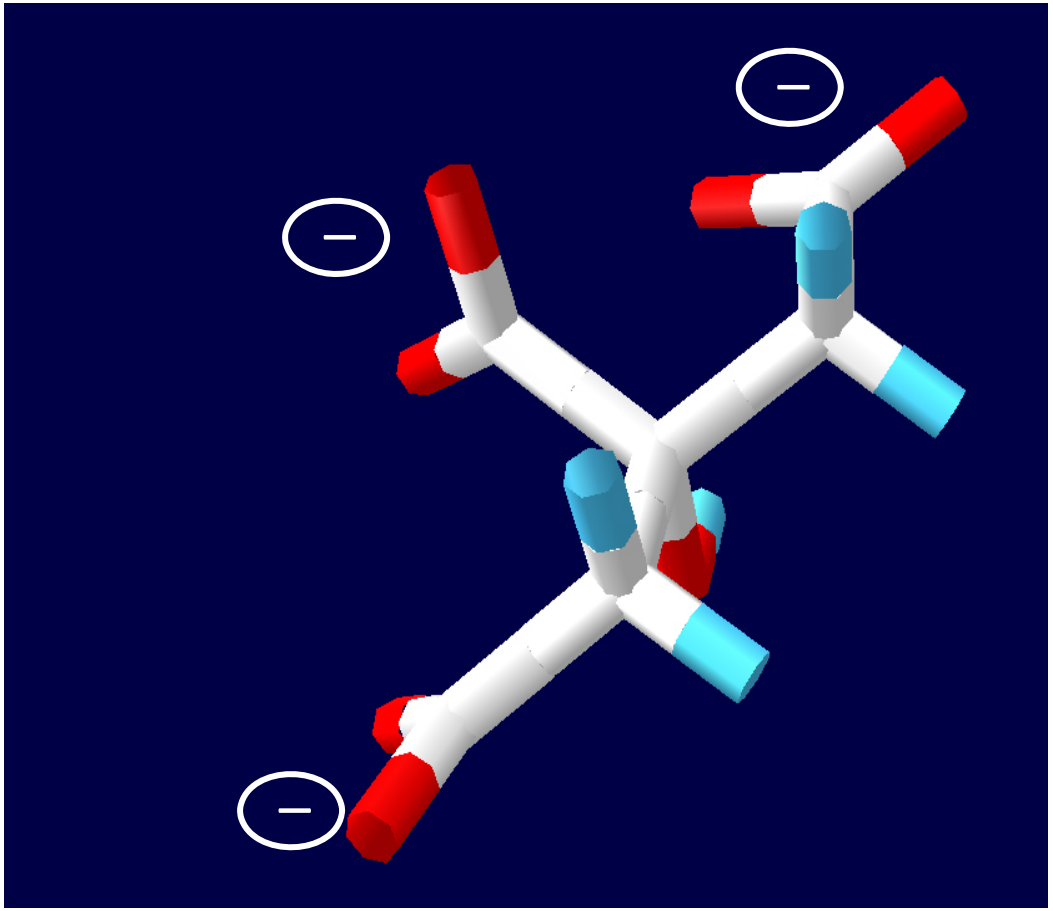
Prevention of circuit clotting without heparin

3. Regional anticoagulation

Citrate / Calcium

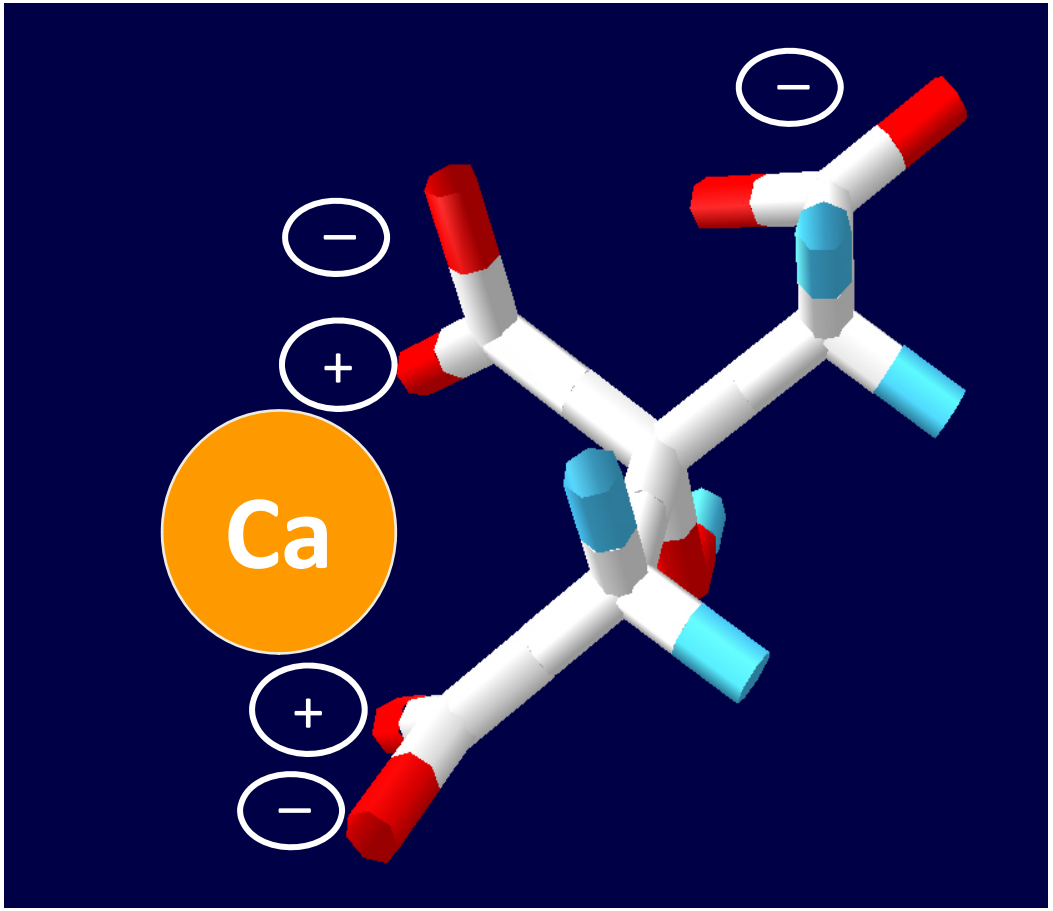
Citrate Anticoagulation

Sodium citrate

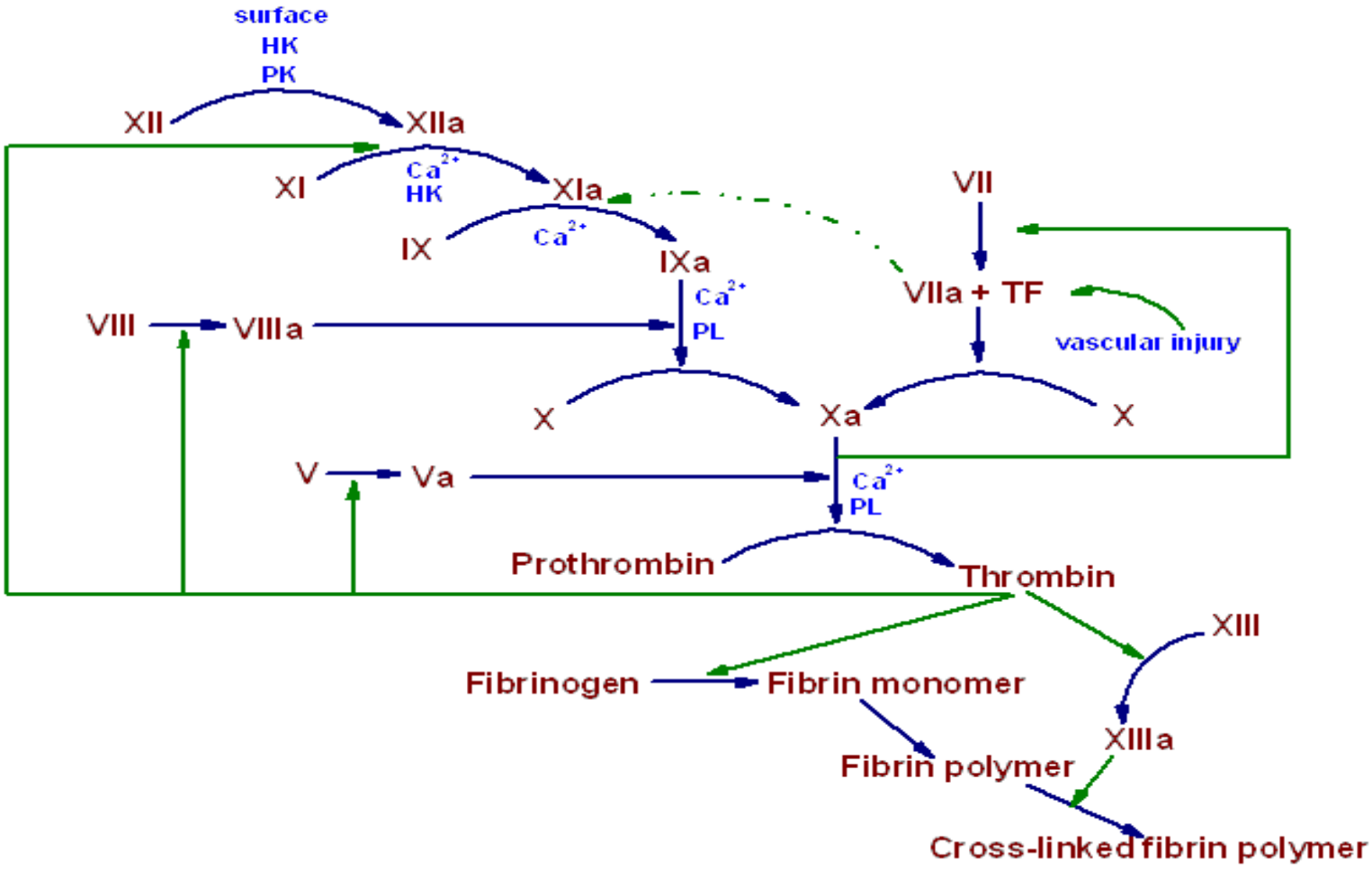


Citrate Anticoagulation

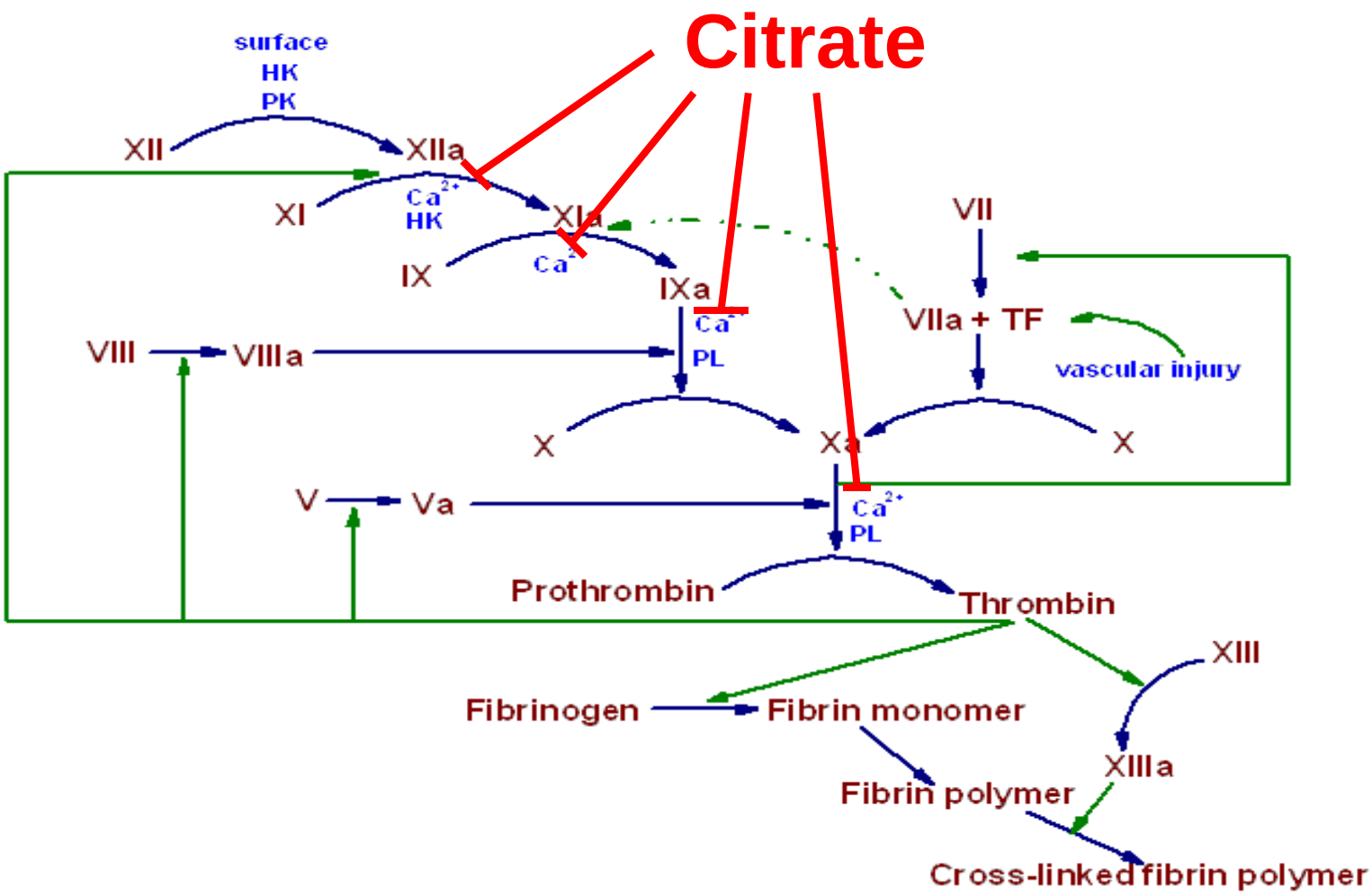
Sodium citrate



Citrate Anticoagulation



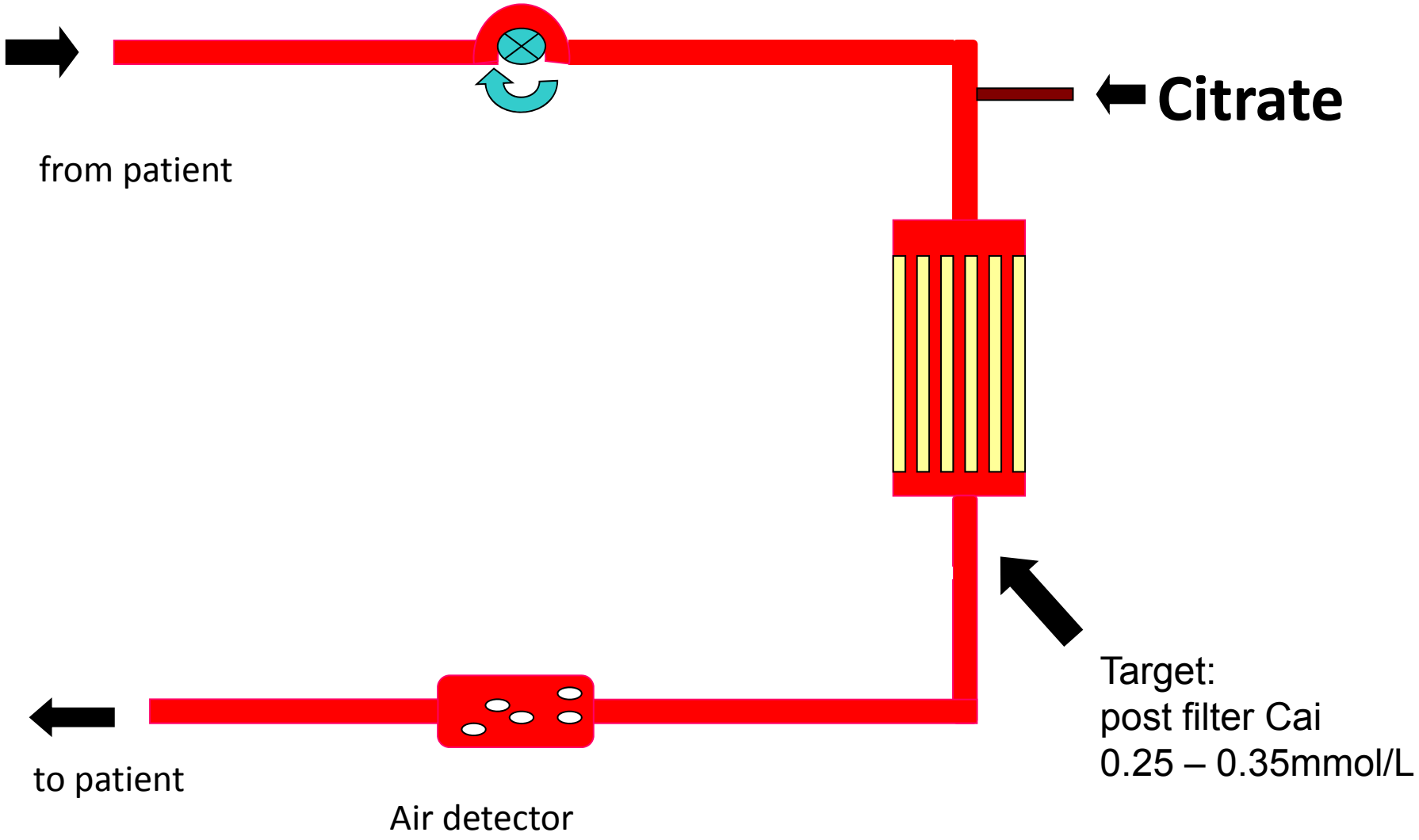
Citrate Anticoagulation



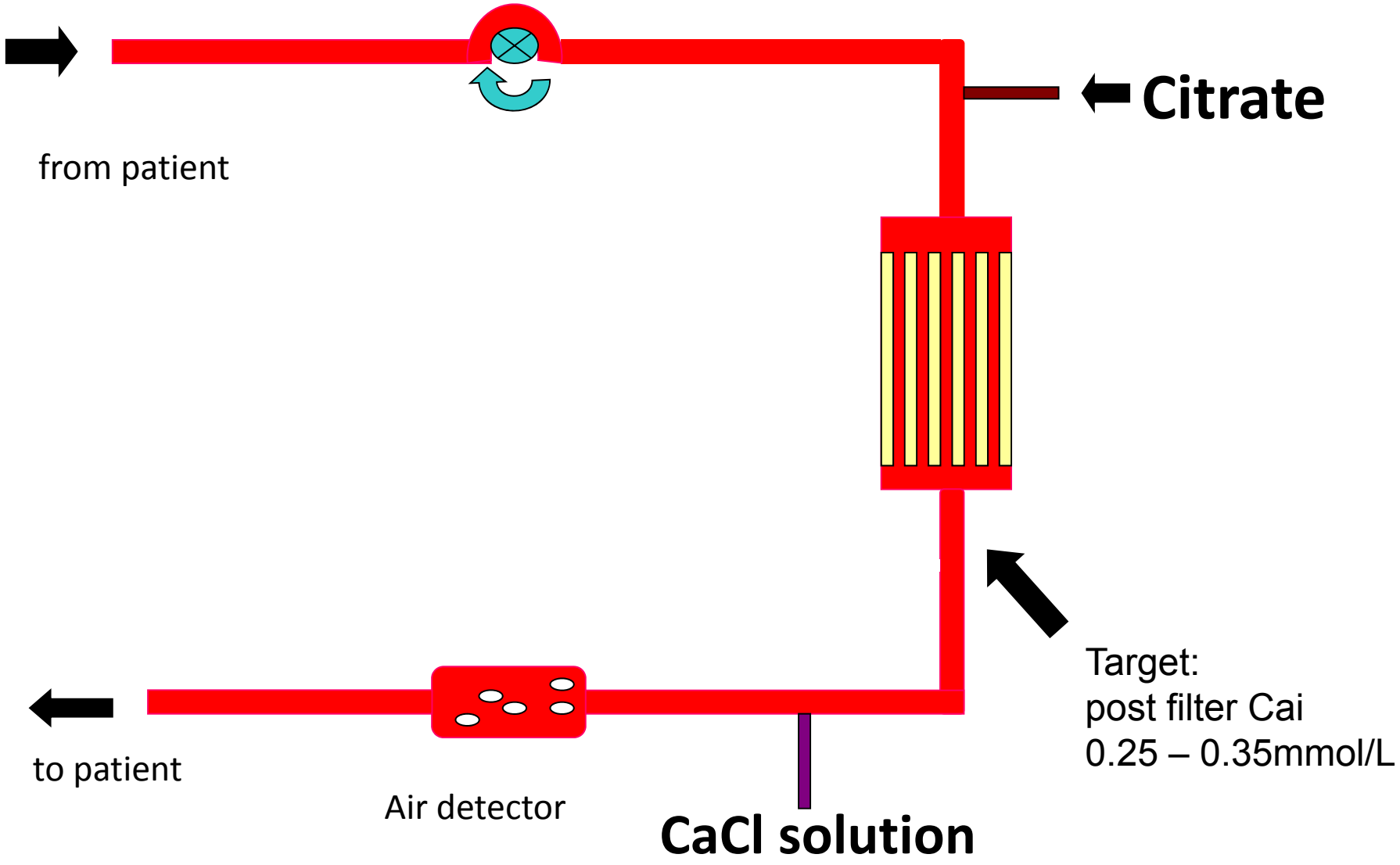
Ionized Ca < 0.5 mmol/L ⟶ clotting cascade impaired

Ionized Ca < 0.3 mmol/L ⟶ clotting cascade completely inhibited

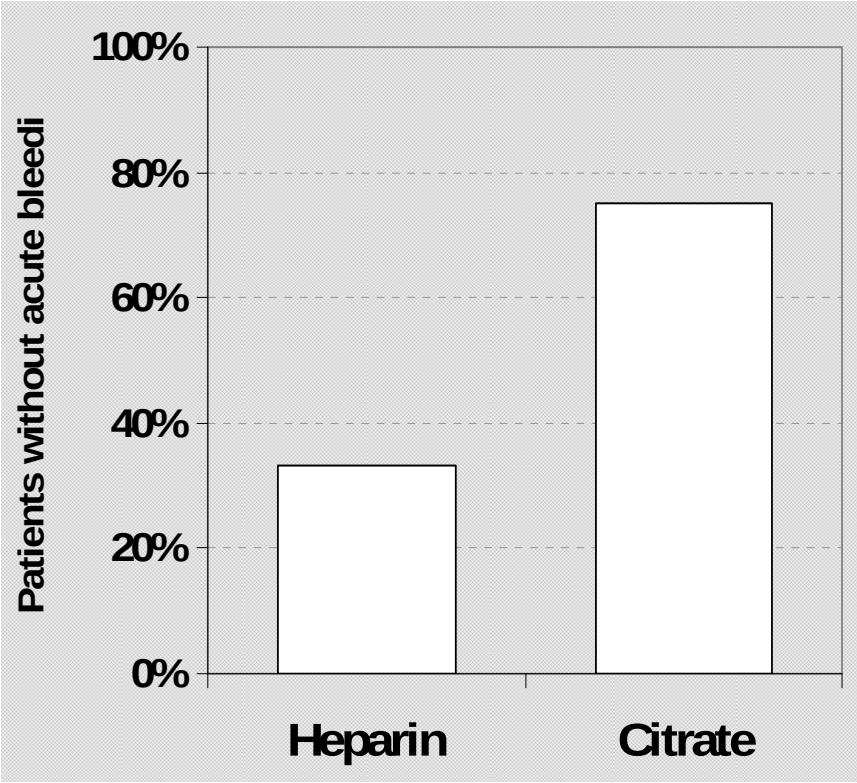
Citrate Anticoagulation

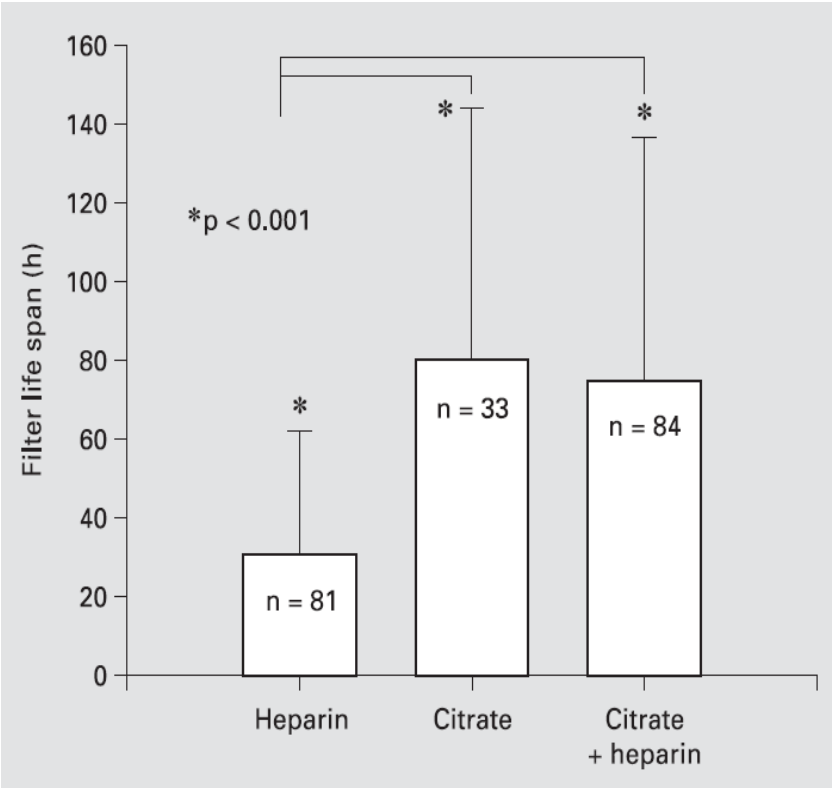


Citrate Anticoagulation



Citrate Anticoagulation





Gabutti et al.
Intensive Care Med 2002

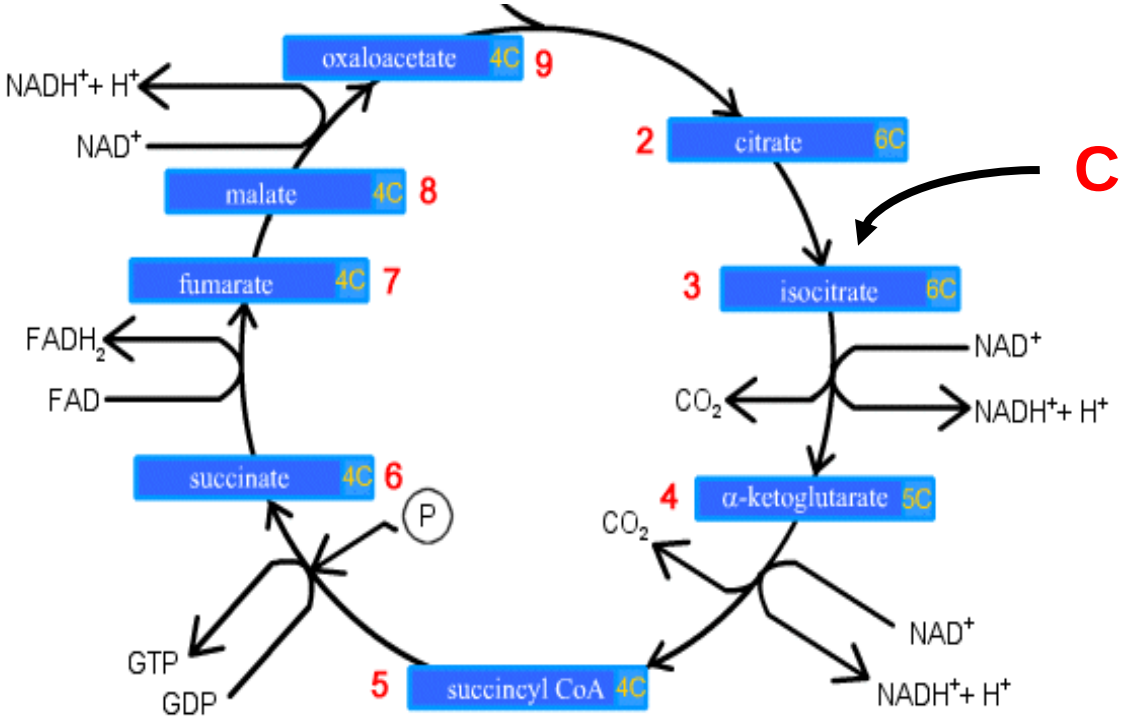
Morgera et al.
Nephron Clin Pract 2004

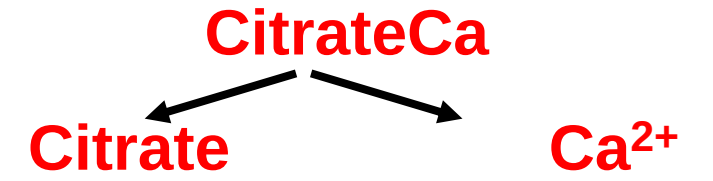
Less bleeding AND prolonged filter life

Citrate anticoagulation

Elimination of citrate:

- ~40-50% cleared across the filter
- ~50-60% eliminated via Krebs cycle in liver and skeletal muscle (and renal cortex)





1 molecule citrate

→ 3 molecules HCO_3

Citrate Anticoagulation

Oudemans-van Straaten *et al. Critical Care* 2011, 15:202
http://ccforum.com/content/15/1/202

REVIEW

Clinical review: Anticoagulation for continuous renal replacement therapy - heparin or citrate?

Heleen M Oudemans-van Straaten[1]*, John A Kellum[2] and Rinaldo Bellomo[3]

Heparin: pro-inflammatory effects
increases risk of bleeding

Citrate: no pro-inflammatory effects
provides energy to mitochondria

Disadvantages of citrate anticoagulation

1. **Metabolic derangements**

   metabolic alkalosis
   hypocalcaemia
   metabolic acidosis (citrate accumulation in liver failure)
   hypomagnesaemia (citrate binds to Mg)
   hypernatraemia

2. **Reduced citrate metabolism in severe liver disease**

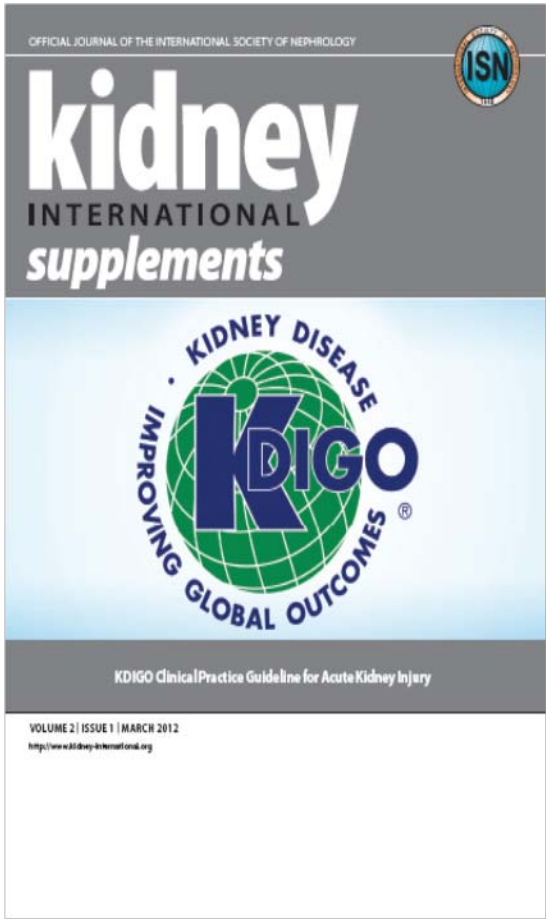
3. **Intolerance in "shock"**

   i) oxygen is essential in Krebs cycle
   ii) patients with intracellular hypoxia and lactic acidosis cannot metabolise citrate → worsening acidosis
   declining serum Ca

4. **Technical complexity**

5. **More expensive than heparin but safe / potentially cost effective**

Citrate Anticoagulation



Chapter 5.2, page 98

"A major contra-indication for the use of citrate anticoagulation is severely impaired liver function or shock with muscle hypoperfusion, both representing a risk of citrate accumulation."

March 2012

Anticoagulation

Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study

Critical Care 2012, **16**:R162

Observational study 2009 – 2011
28 ICU patients (ie. 43 CVVHD sessions) with decompensated CLD or ALF

Results:

- Circuit patency >72h in 74% of CVVHD sessions.
- Up to 29-fold elevated serum citrate levels at 72h
- PT ≤26% and serum lactate ≥3.4 mmol/L associated with citrate accumulation.
- Citrate stopped because of high Ca_T/Ca_i ratio in 3 patients

Conclusion: CVVHD using citrate for regional anticoagulation in liver failure patients is feasible.

Drug dosage

Principles of drug removal

Drug factors:

- Protein binding
- Hydrophilic vs lipophilic
- Volume of distribution
- Method of total body clearance

Molecular size doesn’t matter much

Most drugs < 1000 D

Membrane cut - off: 20 000 – 50 000 D

Principles of drug removal

Protein binding

- Only drugs not bound to plasma proteins will be removed by CRRT
- Binding to Albumin, α_1-acid glycoprotein, lipoprotein
- Drug-protein = 50,000 D

- Additional changes in ICU patients
  - pH
  - Albumin ↓
  - other drugs

Principles of drug removal

Drug dosing in continuous renal replacement therapy: general rules

Miet Schetz

Curr Opin Crit Care 13:645–651.

Principles of drug removal

Protein binding

High (~90%)

- Midazolam
- Ceftriaxone
- Teicoplanin
- Clindamycin
- Amphotericin
- Cyclosporin
- Amiodarone

Low (<15%)

- Meropenem
- Gentamicin
- Fluconazole
- Metronidazole
- Aciclovir
- Lisinopril

Principles of drug removal

Volume of distribution

- Changes in critically ill patients
  - increased volume of distribution, esp in severe sepsis
  - altered protein binding

- only plasma level available for extracorporeal removal (vs interstitial or tissue concentrations)

Principles of drug removal

Pk of Clearance

Total Clearance

(ml/min)

= Cl_{renal} + $Cl_{non\ renal}$ (+ Cl_{filter})

CRRT clearance important if Cl_{renal} >25-30%

Principles of drug removal

Renal clearance

High	**Low** (<25%)
Benzylpenicillin (85%)	Erythromycin
Cefuroxime (96%)	Clindamycin
Ceftazidime (84%)	Amphotericin
Milrinone (80%)	Cyclosporin
Digoxin (65%)	Labetalol
Atenolol (94%)	Hydralazine

Is CRRT clearance important?

	Vd (L/kg)	**% renal**	
Meropenem	0.25	70%	
Gentamicin	0.25	100%	
Fluconazole	0.7	75%	
Metronidazole	0.7	10%	×
Aciclovir	0.7	75%	
Ganciclovir	0.6	90%	
Lisinopril	1.5	100%	

Is CRRT clearance important?

	Protein Binding	Vd (L/kg)	
Benzylpenicillin	60%	0.3	✓
Cefuroxime	33%	0.19	✓
Ceftazidime	21%	0.23	✓
Digoxin	25%	5-8	×
Milrinone	70%	0.3	?
Atenolol	<5%	0.95	✓

Drug removal during CRRT

Additional contributing factors

- Size of filter
- RRT dose
- Membrane interactions

  Adsorption of proteins on membrane

  Gibbs-Donan effect: retention of anionic drugs on protein of membrane
- Interruptions in RRT

Drug removal during CRRT

In practice:

Risk of under- and overdosing

Close relationship with ICU pharmacist
altered pharmacokinetics of drugs
dynamics of clinical condition

Regular review of drug chart

DALI


Defining Antibiotic Levels in Intensive care unit patients

DALI

International multi-centre study sponsored by ESICM grant

Point of prevalence study (Sept 2011)

Aim: to determine whether contemporary antibiotic dosing for critically ill patients is achieving concentrations associated with maximal antibacterial activity

Provisional results:
Large variation!

Nutrition in RRT

Nutrition in RRT

Facts:

- Albumin is poor marker of nutrition in critically ill
- Protein hypercatabolism due to inflammation, stress, and acidosis is common in critically ill patients.
- Patients with AKI often already malnourished on admission to hospitaL (42%)
- Nutritional effects of CRRT:

loss of: glucose

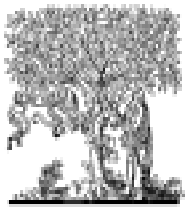
aminoacids and small proteins
(~10-15g amino acids/day ≈ 5-10g protein/day)

trace elements

water soluble vitamins (Vitamin B1, B6, C, folic acid)

Nutrition

Clinical Nutrition (2006) 25, 295–310



ELSEVIER

Clinical Nutrition

http://intl.elsevierhealth.com/journals/clnu

ESPEN GUIDELINES

ESPEN Guidelines on Enteral Nutrition: Adult Renal Failure ☆

N. Cano[a,*], E. Fiaccadori[b], P. Tesinsky[c], G. Toigo[d], W. Druml[e], DGEM: ☆☆ M. Kuhlmann, H. Mann, W.H. Hörl

Nutrition

Summary of statements: Acute renal failure (ARF)

Subject	Recommendations	Grade[71]
General	*Macronutrient* requirements are not so much determined by acute renal failure (ARF) as by the severity of the underlying disease, the type and intensity of extracorporeal renal replacement therapy, and by nutritional status and associated complications: Table 1 Extracorporeal treatment induces increased losses of *micronutrients* which should be supplemented.	
	Monitor micronutrient status because excessive supplementation may result in toxicity.	C
	In ICU patients with ARF, the *electrolyte* content of most 1500–2000 kcal enteral formulae is usually adequate. However, requirements can differ and have to be assessed individually. Plasma electrolyte monitoring should avoid hypokalaemia and/or hypophosphataemia after initiation of enteral nutrition (EN) (refeeding syndrome).	C

Nutrition

aspen
Clinical Guidelines

Journal of Parenteral and
Enteral Nutrition
Volume 33 Number 3
May/June 2009 277-316

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient:

Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

I2. Patients receiving hemodialysis or continuous renal replacement therapy (CRRT) should receive increased protein, up to a maximum of 2.5 g/kg/d. Protein should not be restricted in patients with renal insufficiency as a means to avoid or delay initiation of dialysis therapy. (Grade: C)

Nutrition

KDIGO

3.3.5: We suggest providing nutrition preferentially via the enteral route in patients with AKI. (2C)

3.3.2: We suggest a total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI. (2C)

Nutrition

3.3.3: We suggest to avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT. (2D)

3.3.4: We suggest administering

0.8–1.0 g/kg/d of protein in noncatabolic AKI patients (2D)
1.0–1.5 g/kg/d in patients with AKI on RRT (2D)
and up to 1.7g/kg/d in patients on CRRT and in hypercatabolic patients. (2D)

No comment about supplementation of vitamins or trace elements.

Conclusions

1. Access

1st choice: right jugular vein 2nd choice: femoral vein

3rd choice: left jugular vein

2. Anticoagulation

increasing popularity of citrate anticoagulation

3. Drug dosing

complex

still a lot of uncertainty

DALI may provide new answers

4. Nutrition

enteral nutrition

ensure adequate protein intake

lack of evidence for routine supplementation with vitamins and trace elements