Acute kidney injury and sepsis

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Content

Definition of AKI

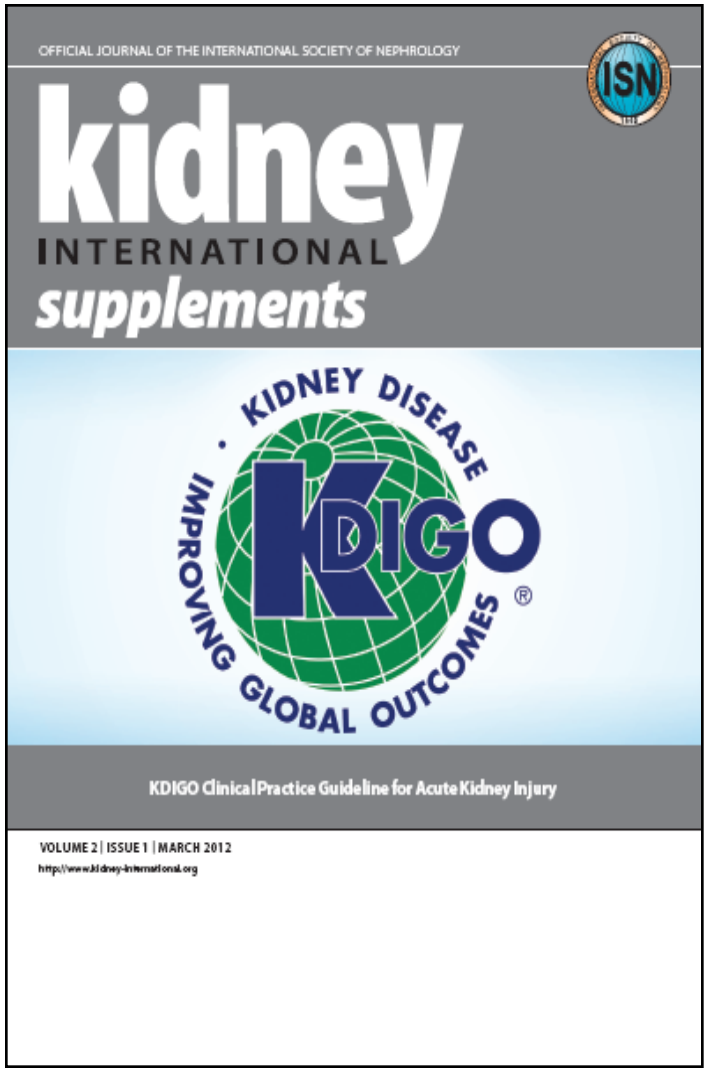
Impact of AKI

RRT

Drug dosing in AKI

Blood purification in sepsis

Definition of AKI



March 2012

KDIGO classification

Aim:

To harmonise RIFLE and AKIN criteria and to agree on **ONE** universal definition

Kidney International 2012; Vol 2: 1 - 141

KDIGO classification of AKI

	Serum creatinine	Urine output
Definition of AKI	AKI is diagnosed if serum creatinine ≥26.5µmol/l over ≤48h OR rises to ≥1.5-fold from baseline in the preceding 7 days	<0.5 ml/kg/h for 6 hours

http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf

KDIGO classification of AKI

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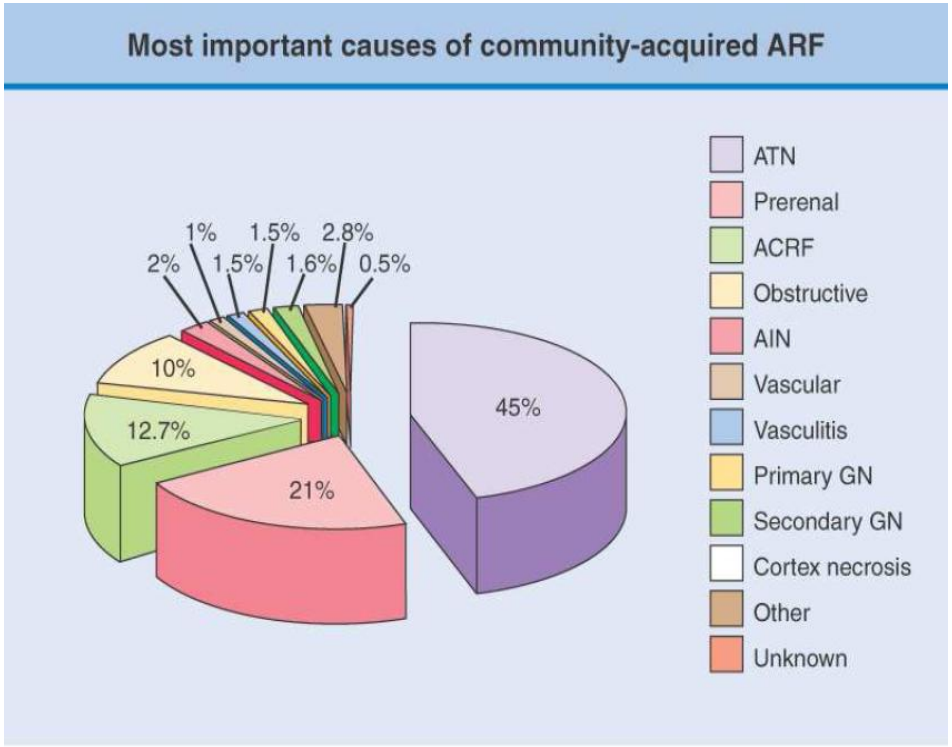
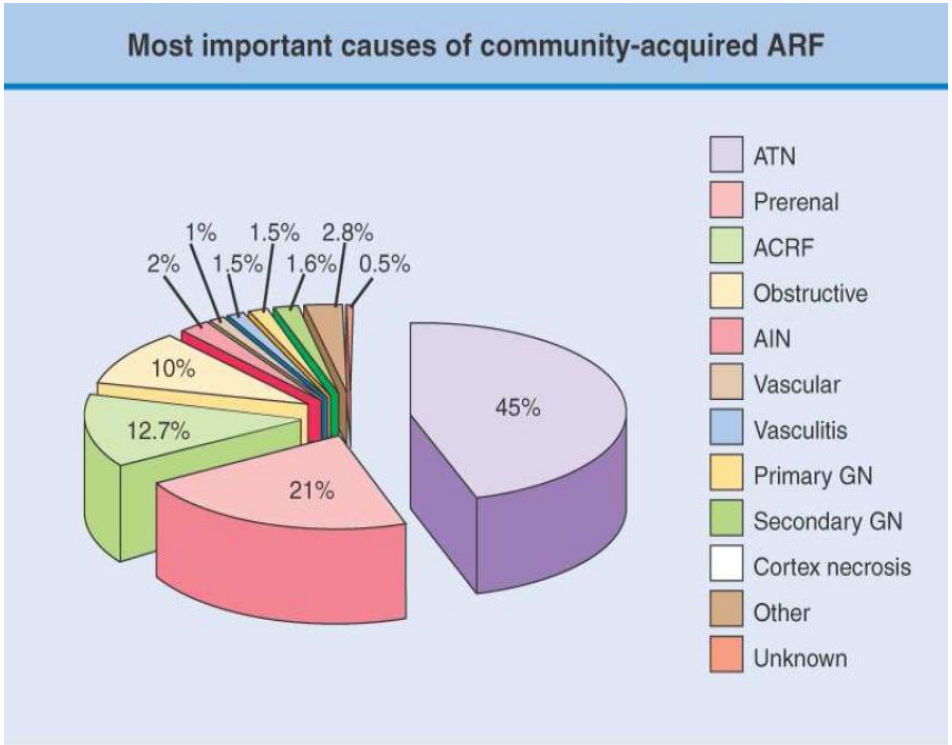
Definition of AKI	AKI is diagnosed if serum creatinine ≥26.5µmol/l over ≤48h OR rises to ≥1.5-fold from baseline in the preceding 7 days	<0.5 ml/kg/h for 6 hours
Stage 1	Creatinine rise ≥26.5µmol/l in 48h OR 1.5-1.9 times from baseline	<0.5ml/kg/h for 6-12 hours
Stage 2	Creatinine rise 2.0-2.9 times from baseline	<0.5ml/kg/h for ≥12h
Stage 3	Creatinine rise ≥ 3 times from baseline, OR rise to ≥353.6µmol/l OR RRT irrespective of serum creatinine	<0.3ml/kg/h for ≥24h OR anuria for ≥12h

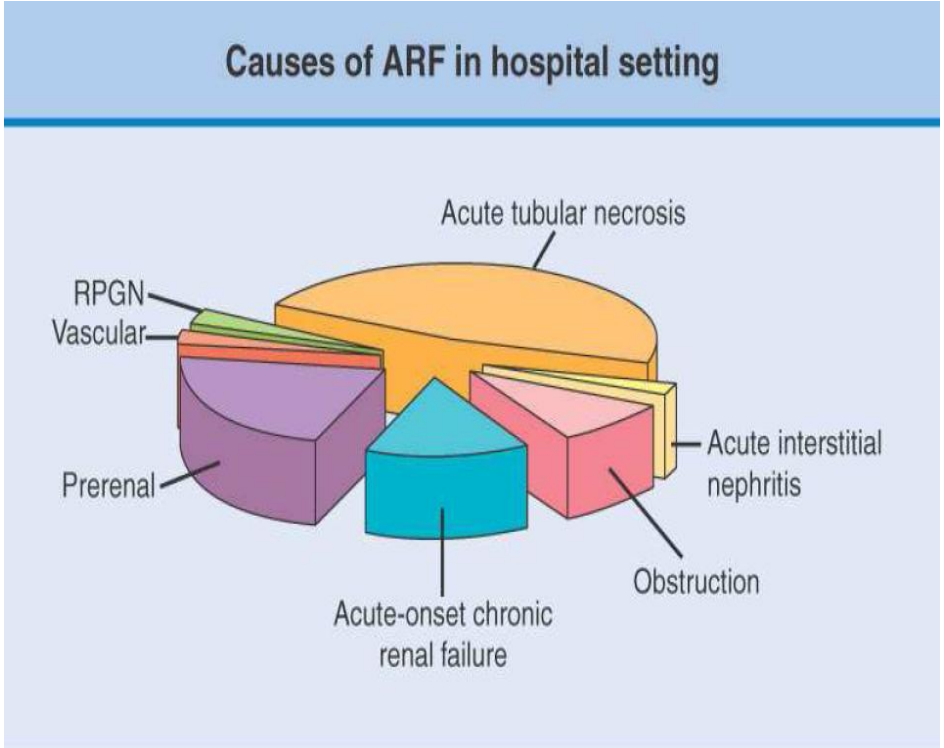
http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf

Causes of AKI



Causes of AKI

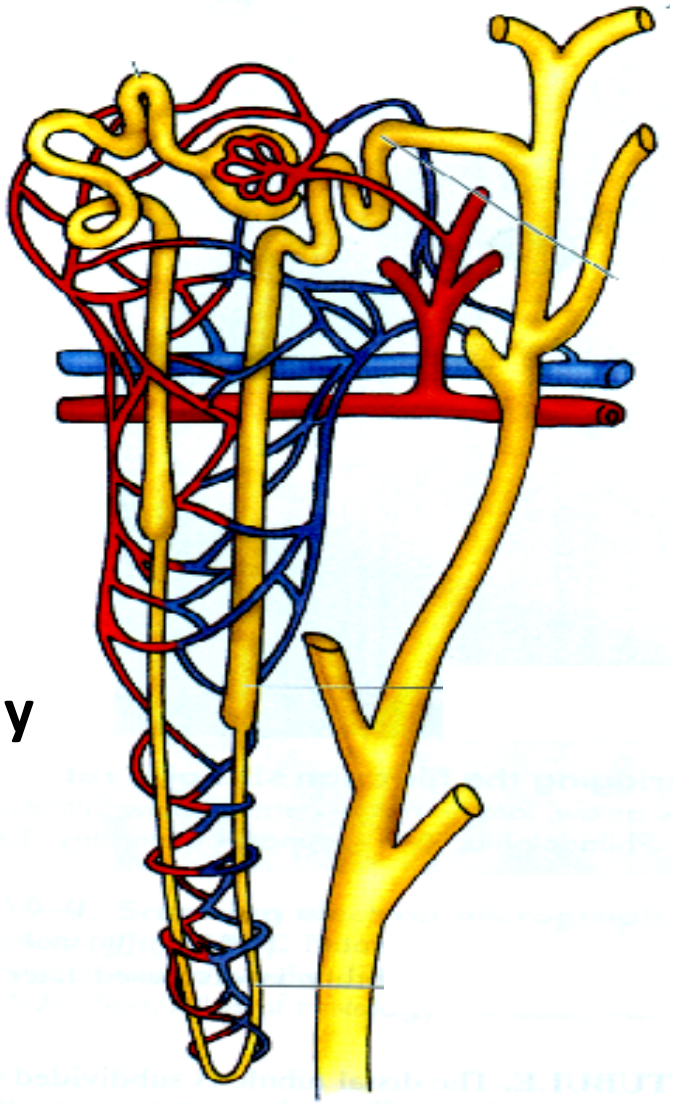




Pathogenesis

Physiology

Close network between tubules and peritubular vessels to balance nutrient and O2 supply with demand



Oxygenation

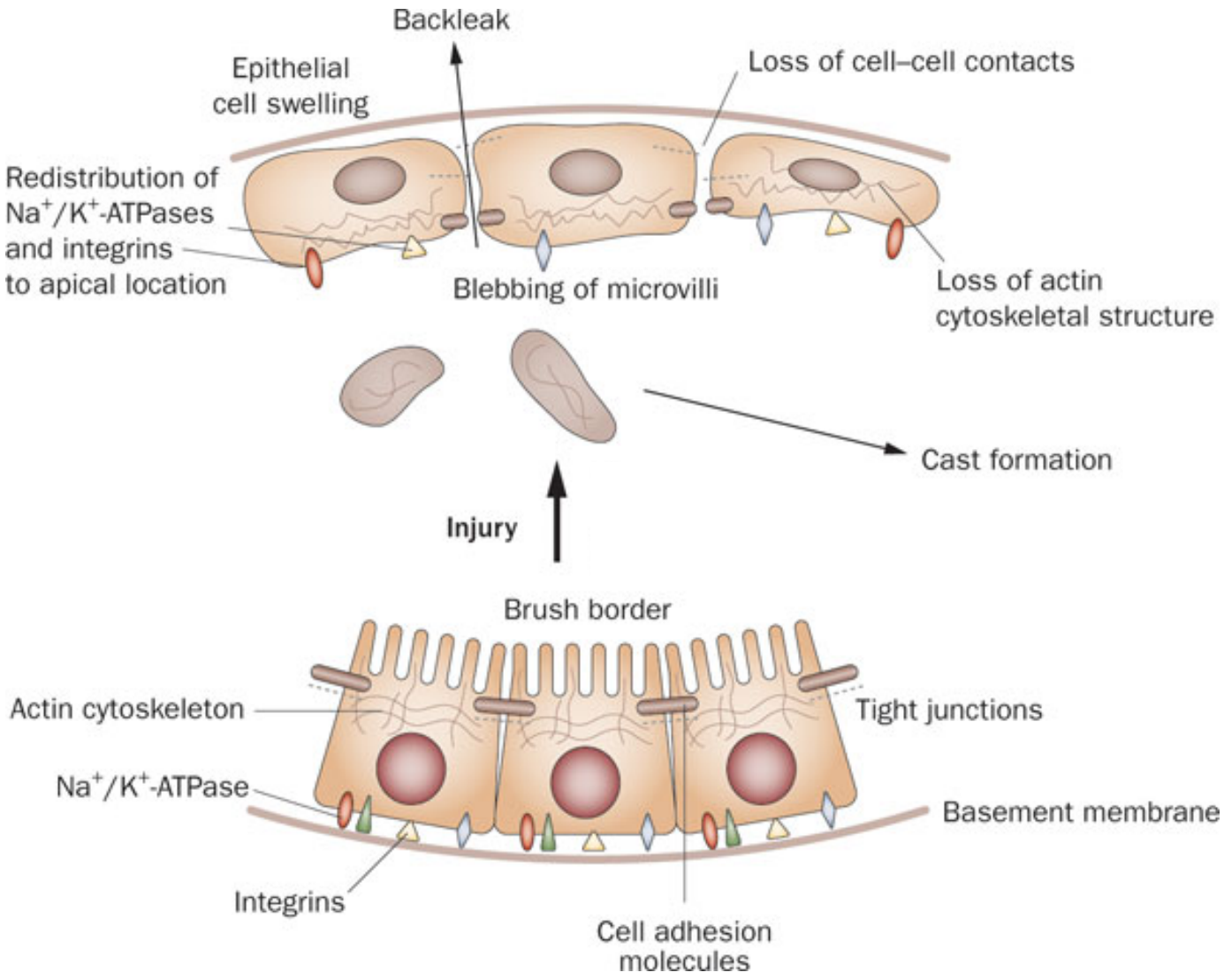
pO_2 6.5 -13.5

pO_2 3 - 6

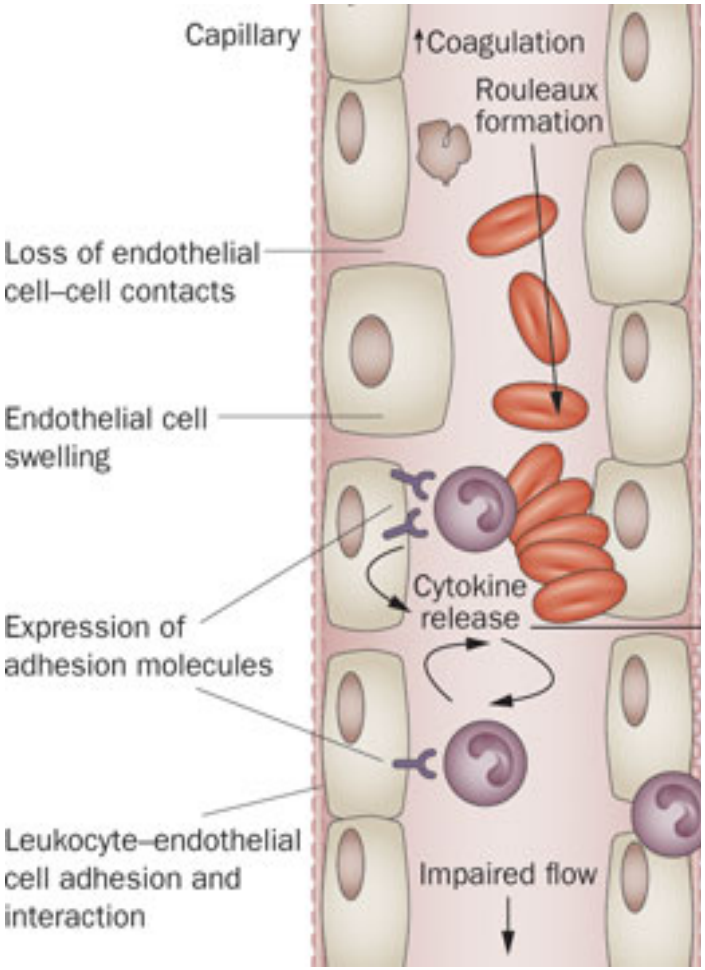
pO_2 1.3 – 2.6

Physiologic medullary hypoxia

Tubular injury

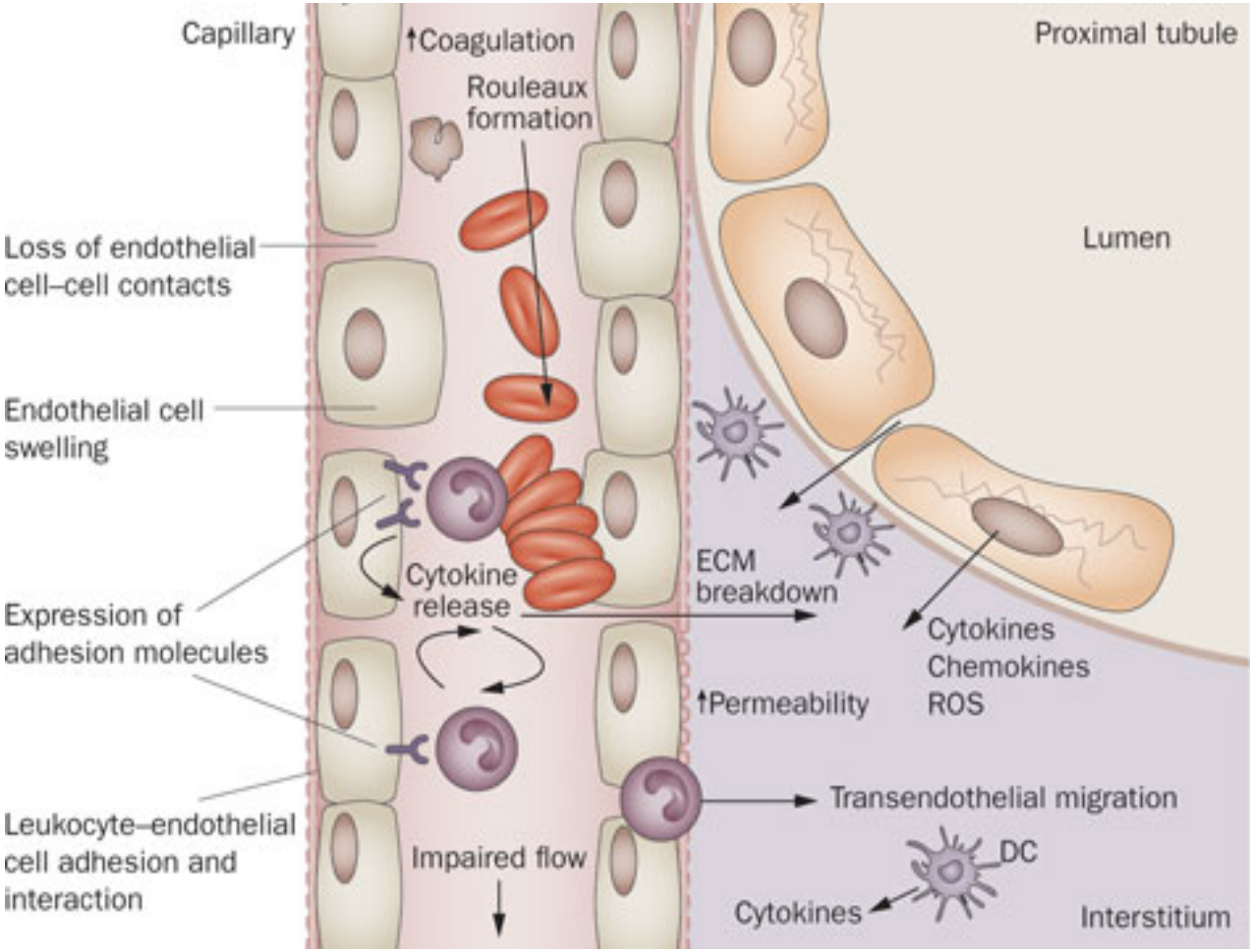


Interstitial inflammation



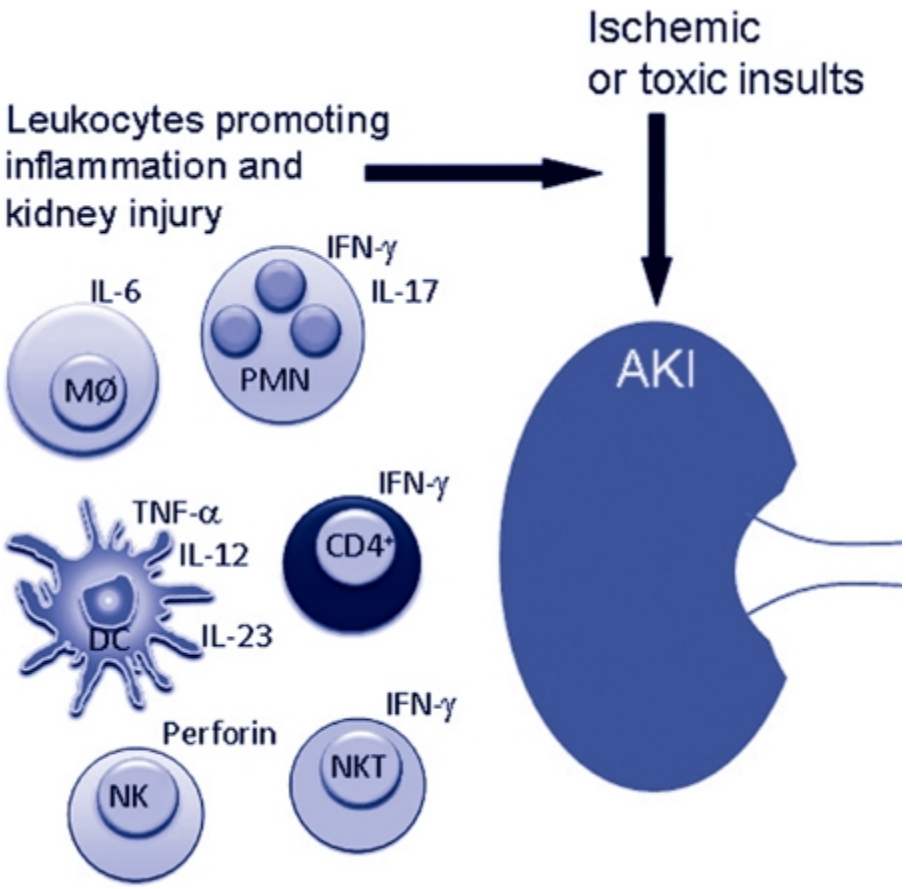
Sharfuddin & Molitoris. Nat Rev Neprol 2011

Interstitial inflammation



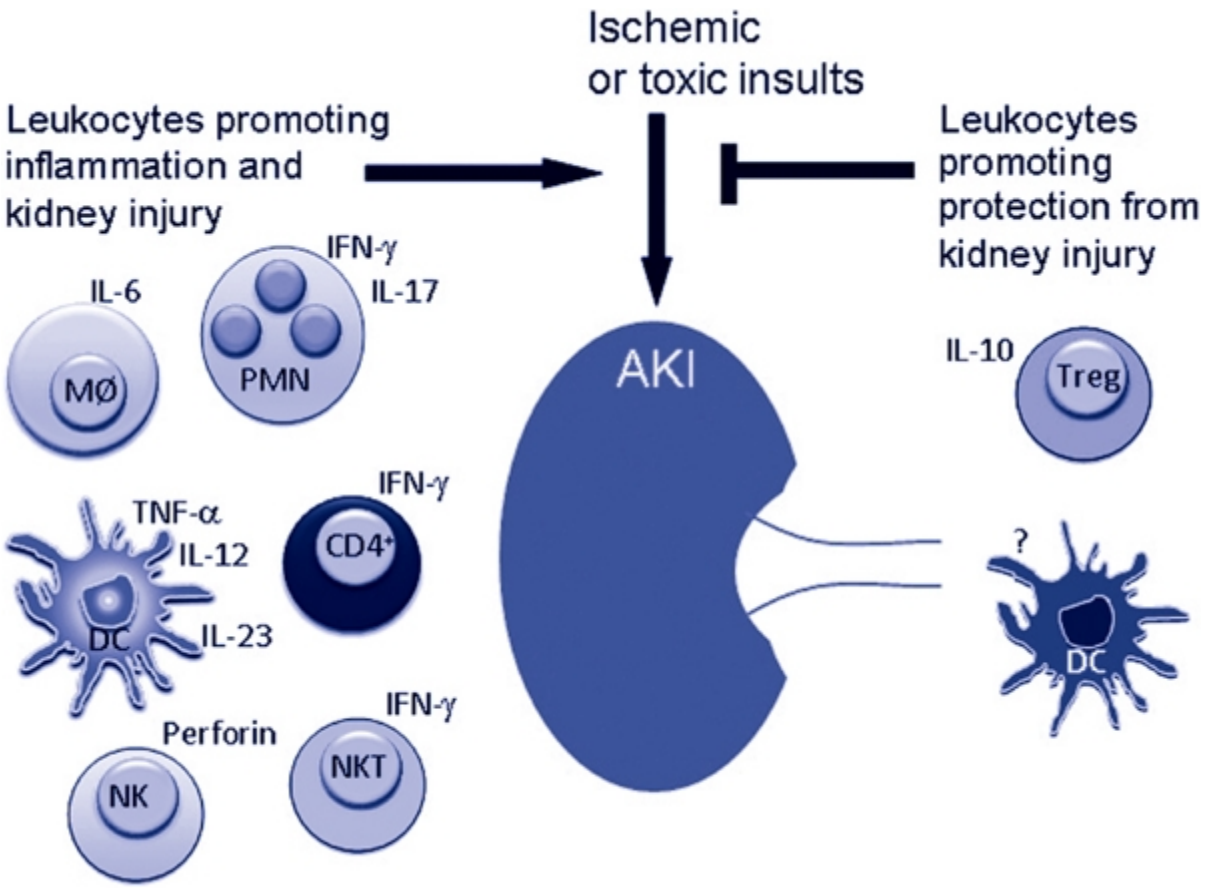
Sharfuddin & Molitoris. Nat Rev Neprol 2011

Inflammation / repair



Kinsey GR et al. Crit Care 2012;16(2)

Inflammation / repair

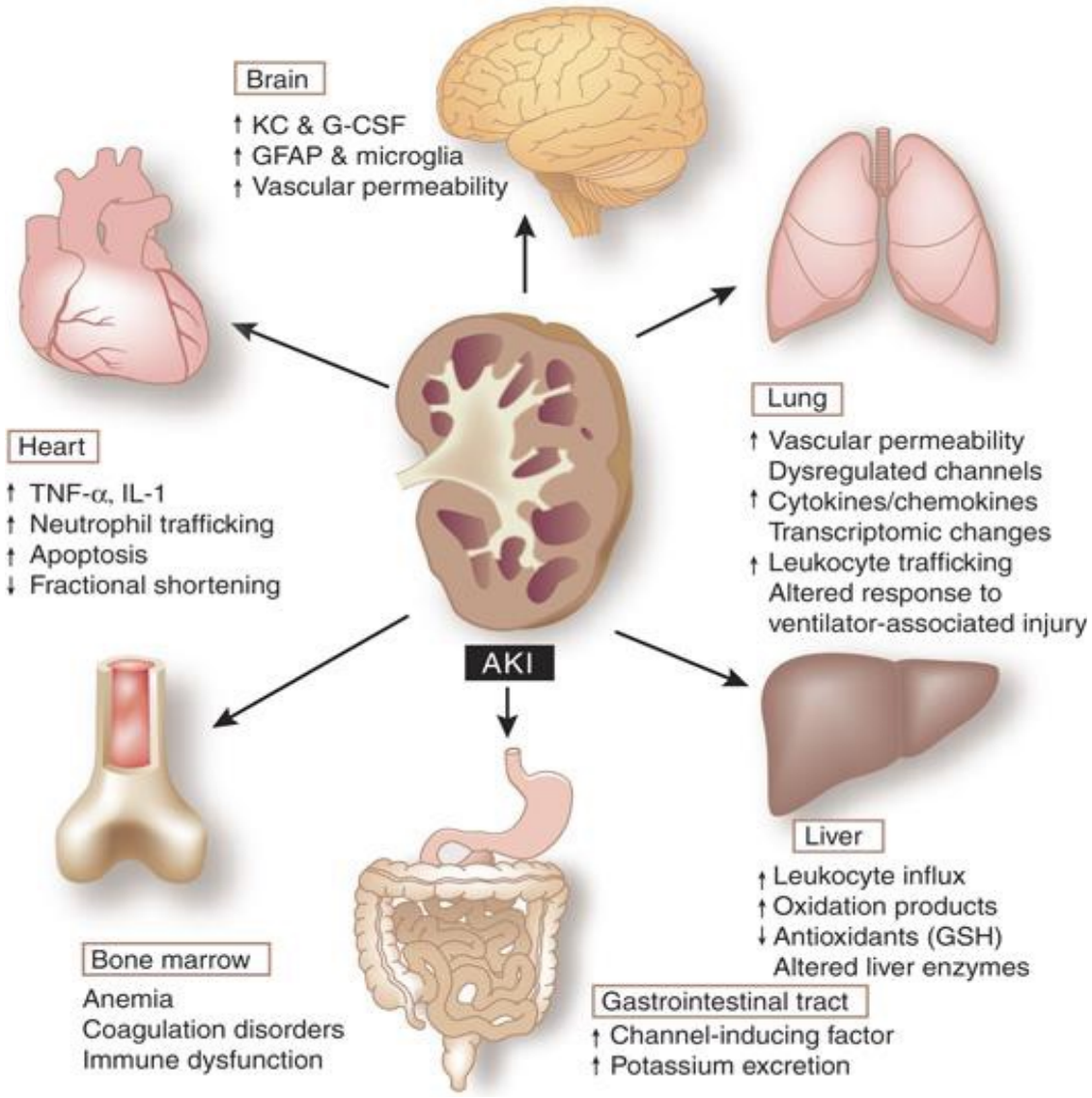


AKI = inflammatory condition

Kinsey GR et al. Crit Care 2012;16(2)

Impact of AKI

Impact of AKI



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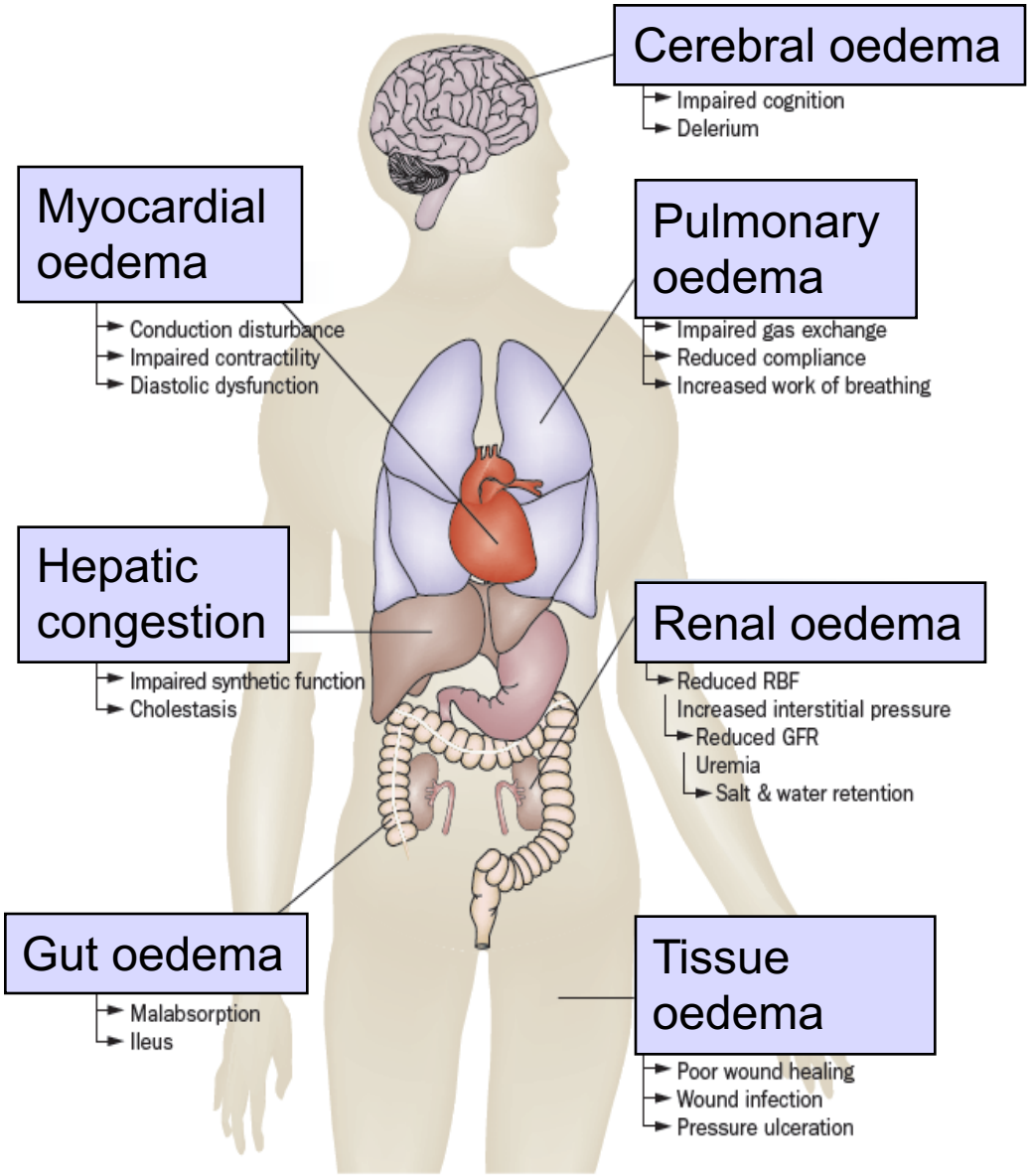

Fluid overload

Prowle J et al. Nat Rev Nephrol 2010;6

Types of RRT

CRRT

continuous veno-venous haemofiltration
continuous haemodialysis
continuous veno-venous haemodiafiltration
peritoneal dialysis

Intermittent RRT

intermittent haemodialysis
slow extended dialysis (SLED) / prolonged intermittent RRT (PIRRT)
SLED-F

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peritoneal dialysis

Intermittent RRT

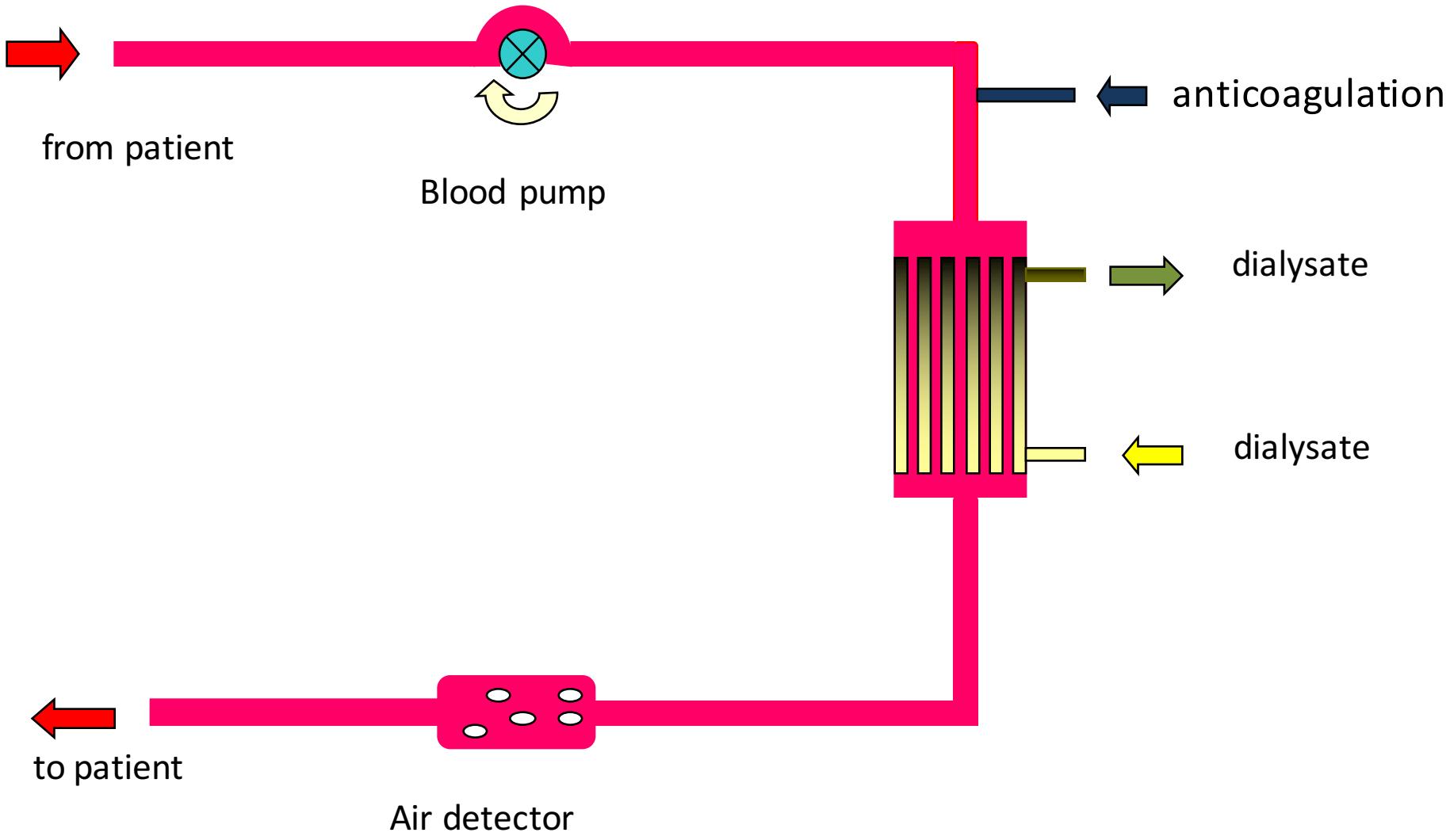
intermittent haemodialysis
slow extended dialysis (SLED) / prolonged intermittent RRT (PIRRT)
SLED-F

Aims:

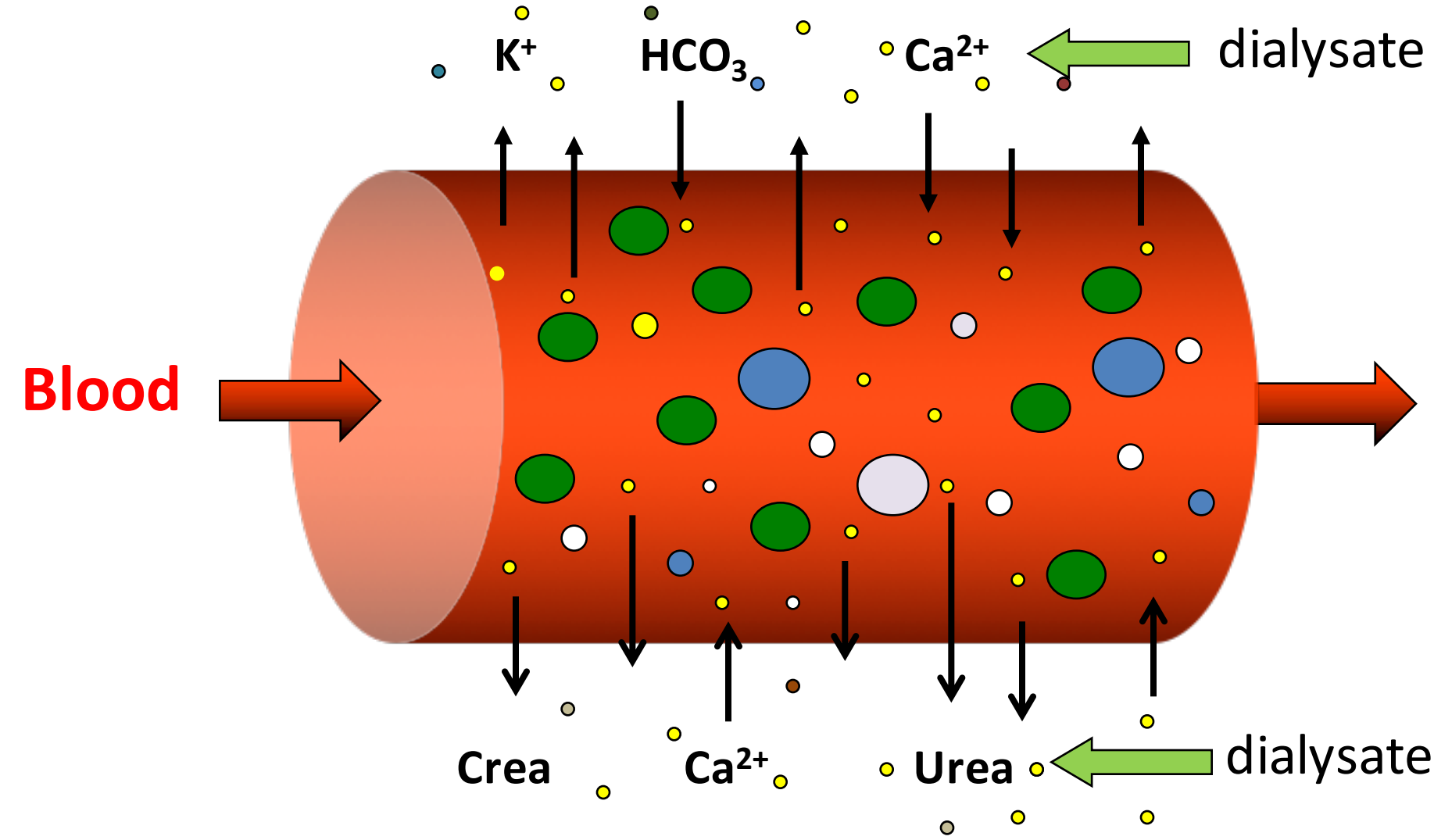
To correct metabolic acidosis
To remove fluid
To remove uraemic “toxins”

Management of RRT in ICU: Mode

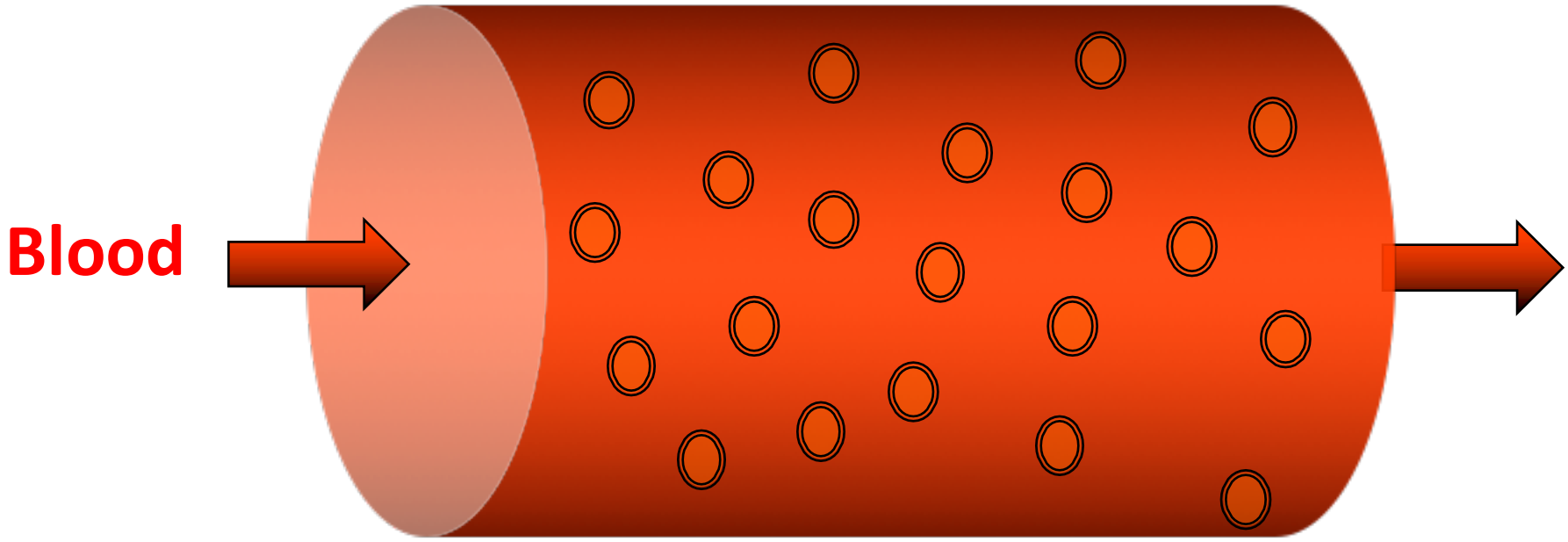
Management of RRT in ICU: Mode



Haemodialysis: Principle of diffusion



Haemofiltration: Principle of convection



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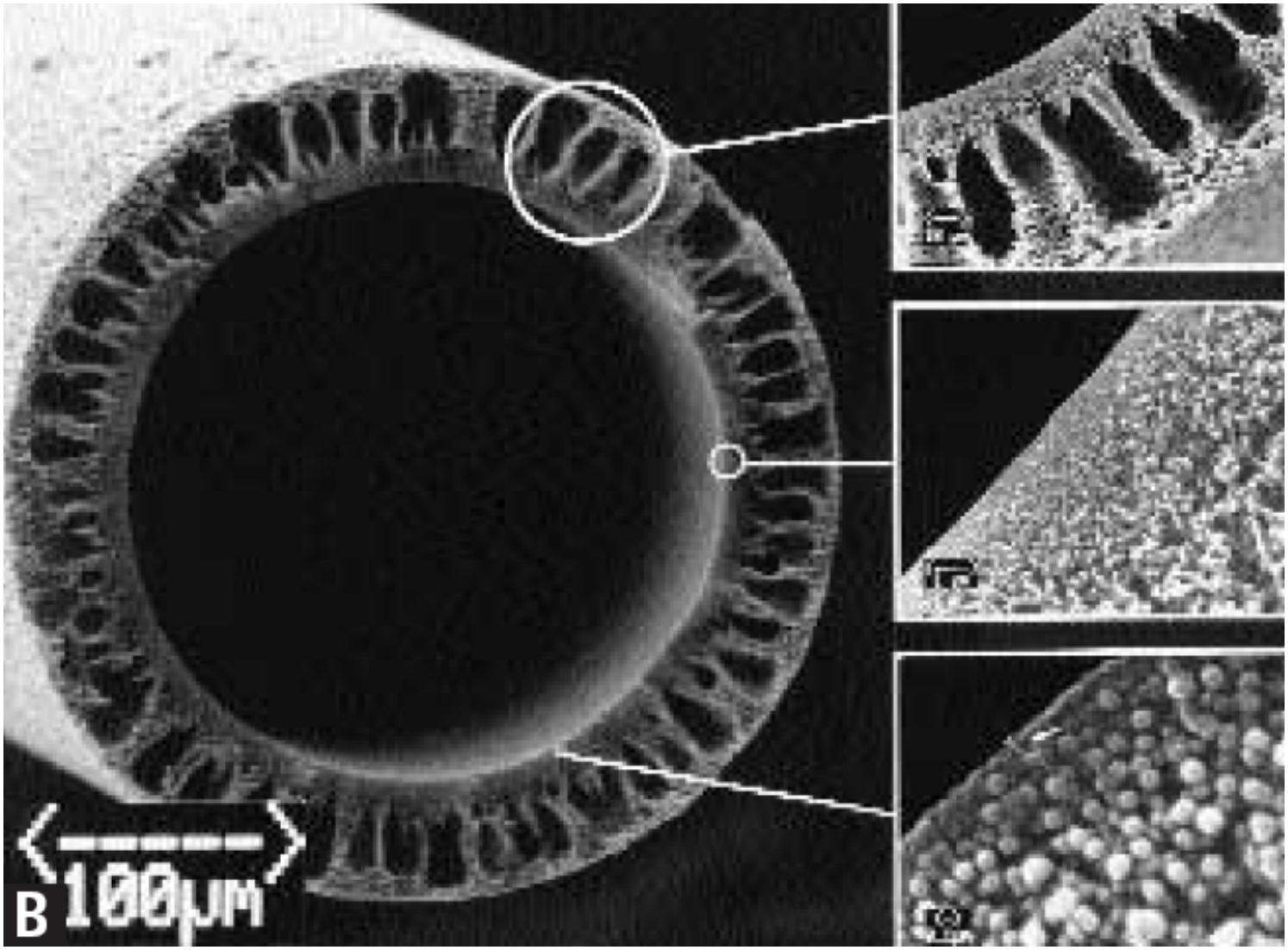

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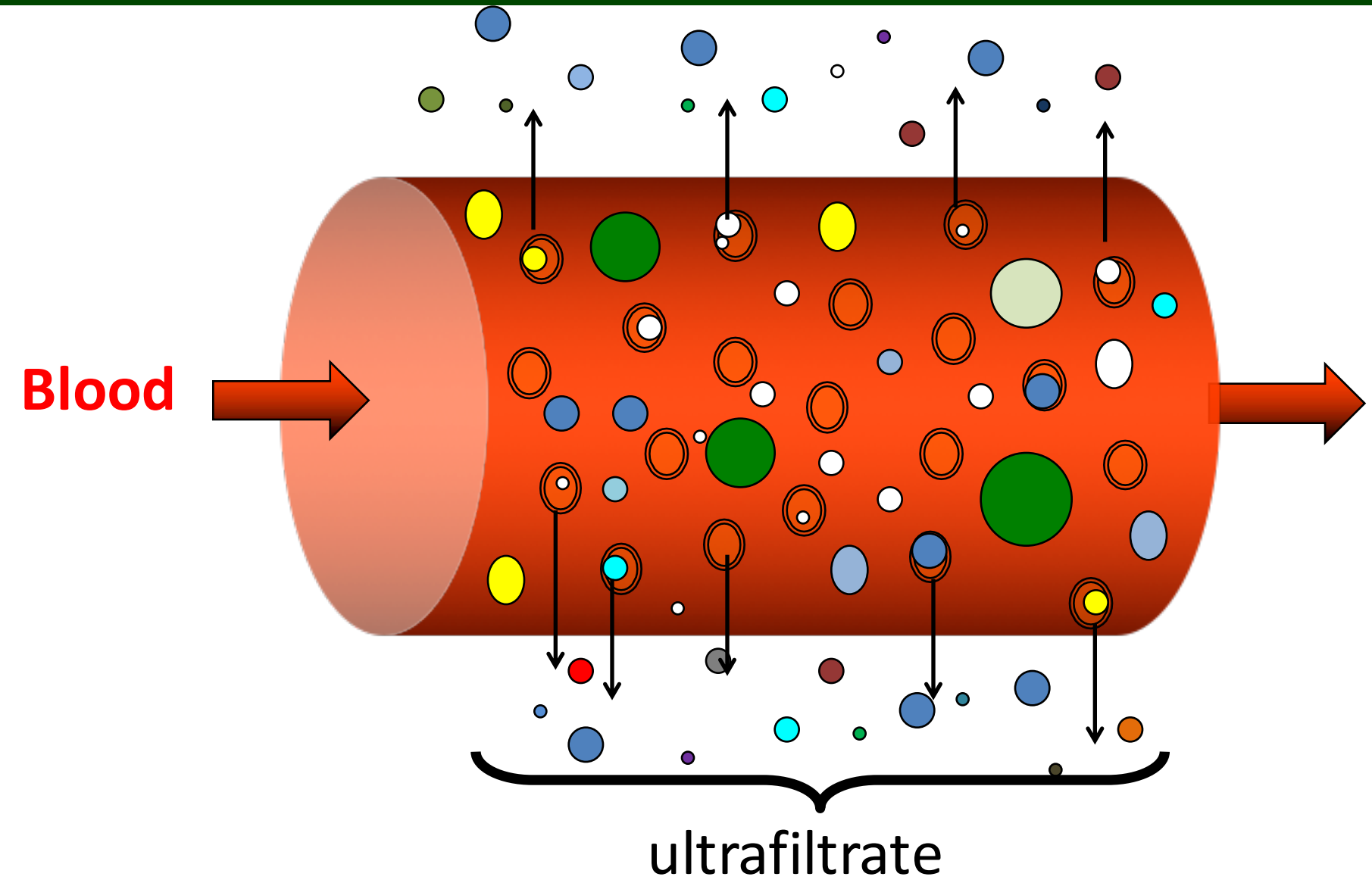

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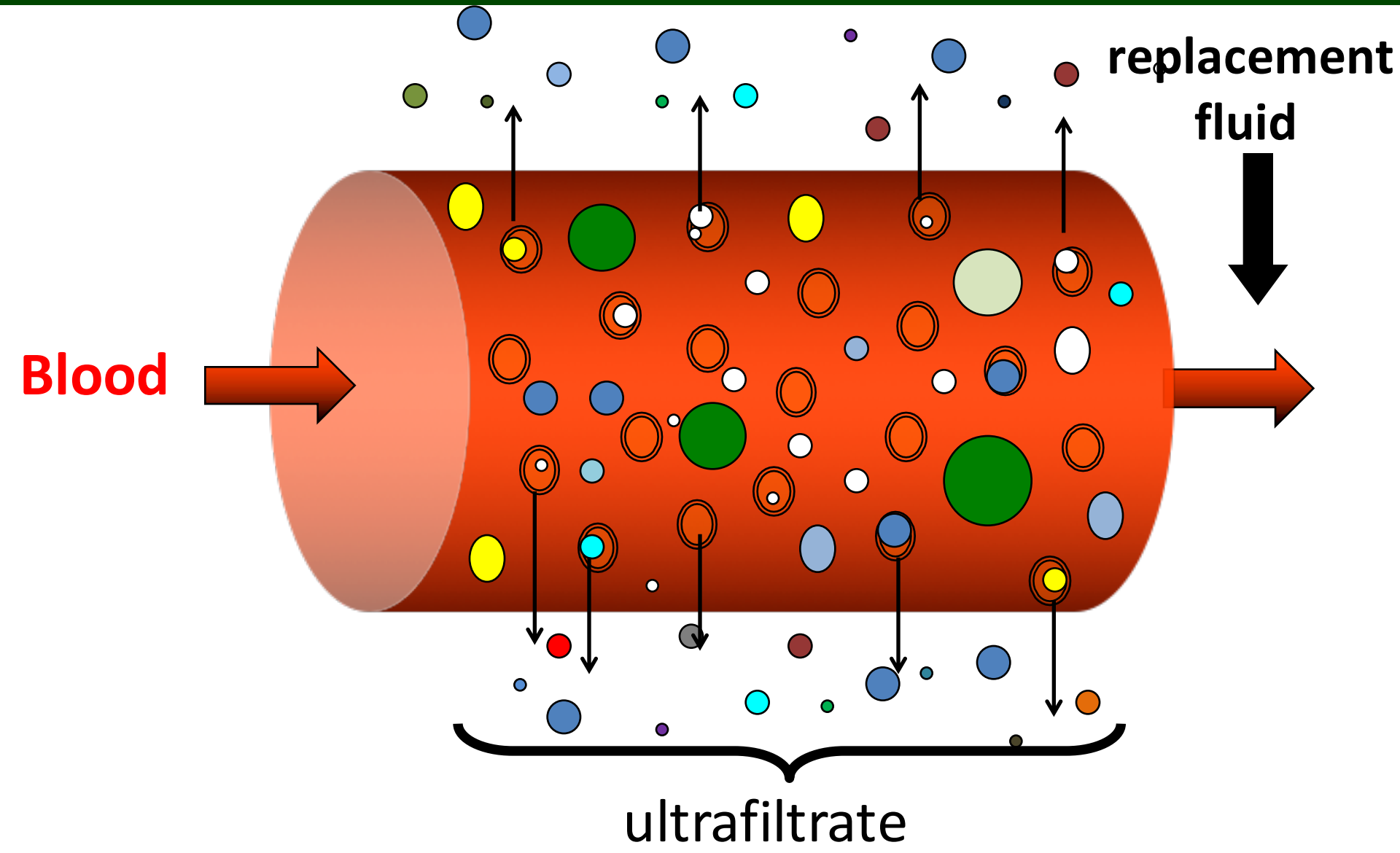

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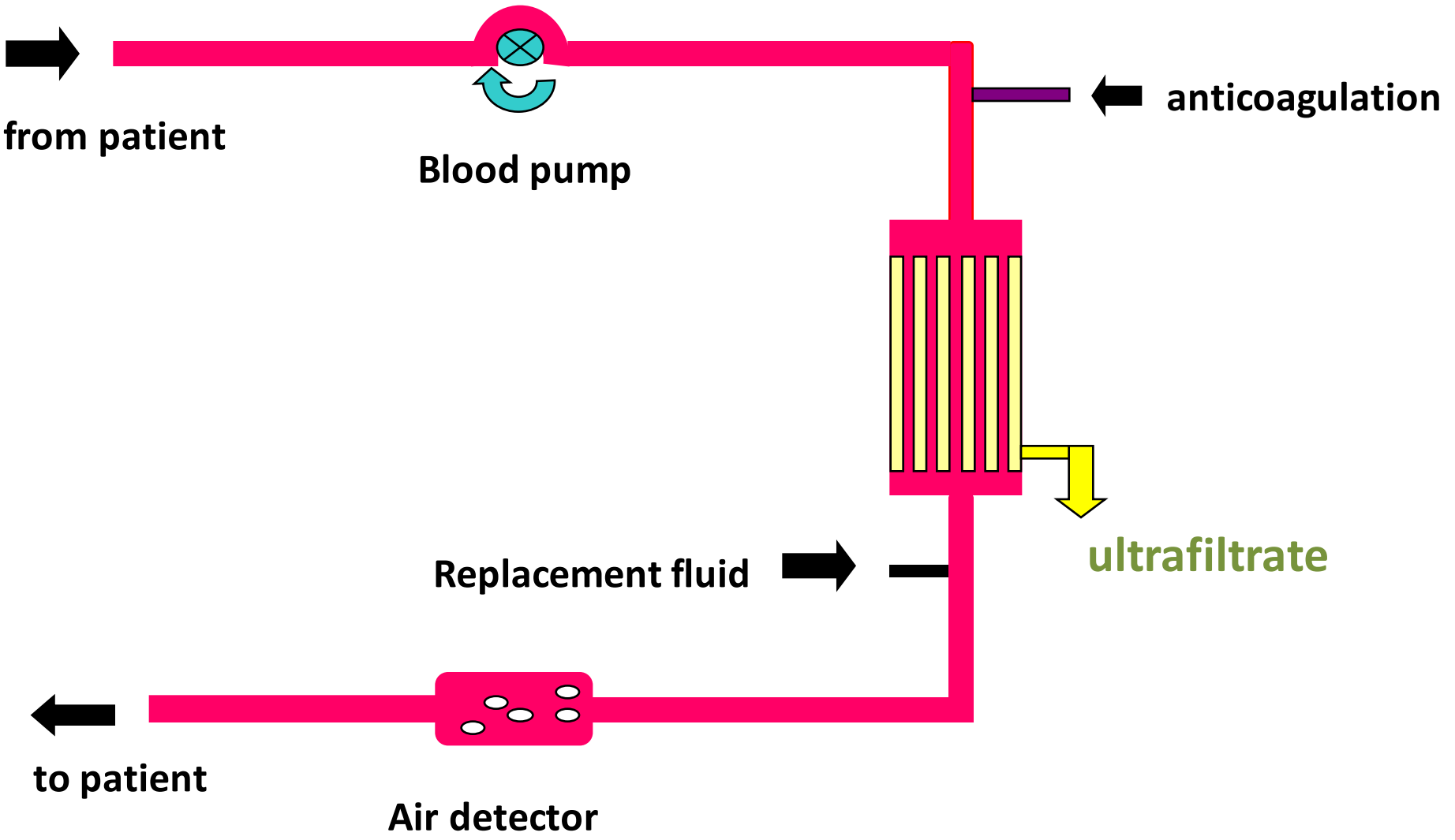
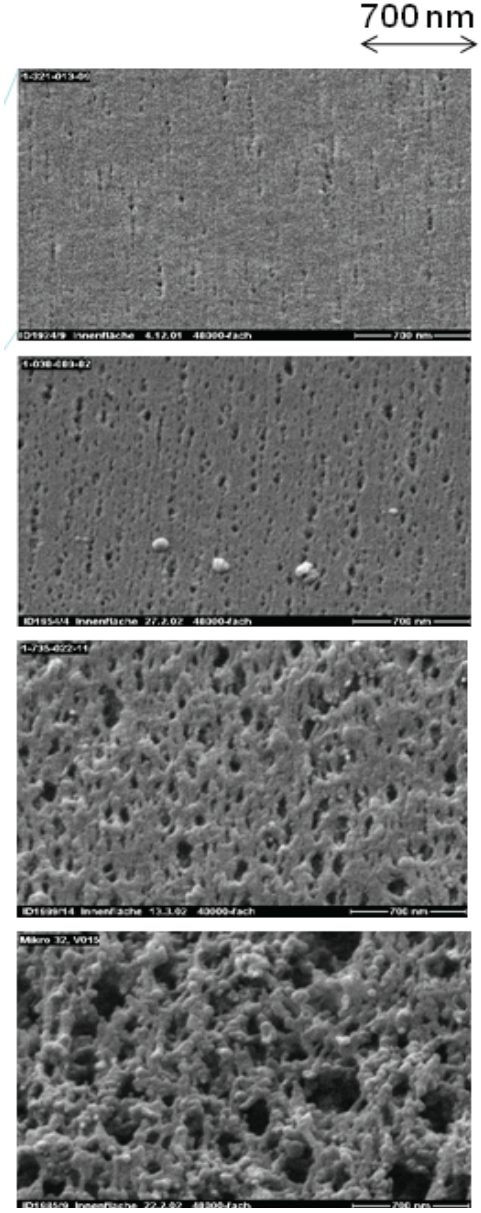


Types of membranes

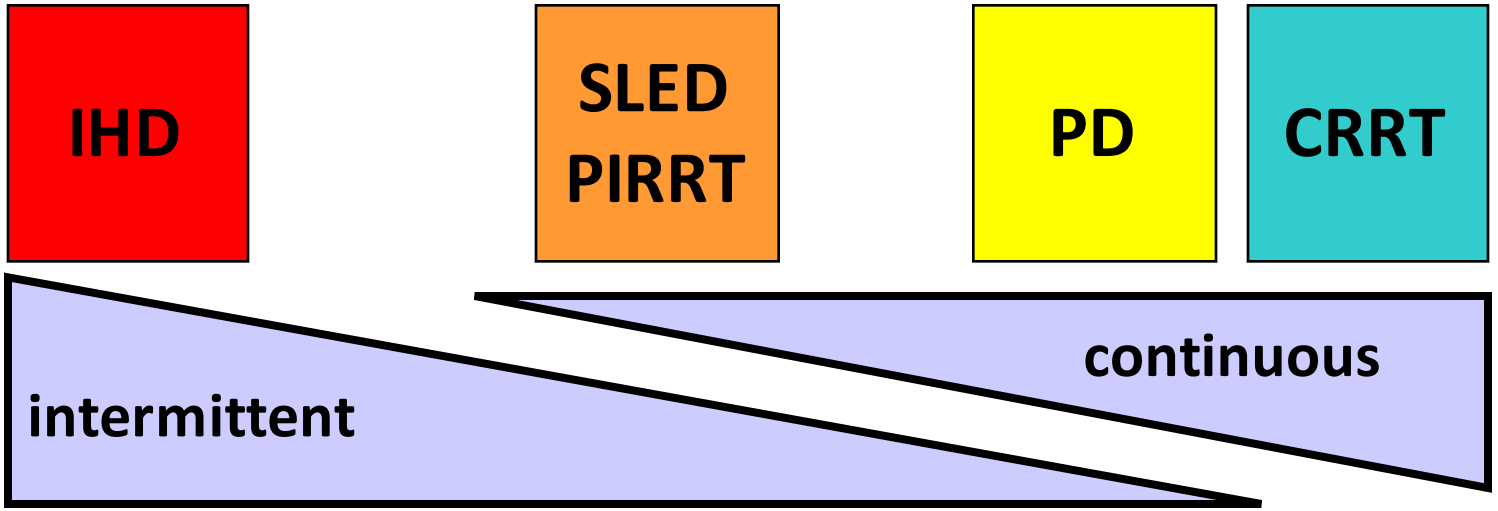


Pore diameter	Type of membrane
< 0.01 µm	High flux
< 0.02 µm	High cut-off
0.09 µm	For protein separation
0.30 µm	Plasma filter

Comparison of modalities

Haemofiltration	Haemodialysis
Convection via highly highly porous membrane (+ some diffusion + absorption)	Diffusion via semipermeable membrane
allows removal of water	allows removal of water
allows removal of substances up to 50,000 Daltons (and even higher)	allows removal of substances up to 30,000 Dalton
usually continuous	continuous or intermittent

Continuous versus intermittent RRT



Clearance per hour +++ ++ +

Fluid shifts

Changes in urea/NH_3/Na^+

RRT in practice

Different modalities

Different types of membranes

Periods on and off RRT (planned and unplanned interruptions)

Different degrees of underlying residual renal function

Drug dosing

Problems in critical illness

Liver / renal dysfunction	→	altered clearance, ↑half life of drugs
Fluid overload	→	increased volume of distribution
Altered pH	→	altered protein binding
Hypoproteinaemia	→	increased amount of “free” drug available

Principles of drug removal

- Difficult as PK alteration in critical illness
- Different modes have different PK parameter

Drug factors:

- Protein binding
- Volume of distribution
- Method of total body clearance (Cl)

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 (↓)
  - bilirubin
  - other drugs

Principles of drug removal

Protein binding

High (~90%)

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

Low (<15%)

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

Principles of drug removal

Volume of distribution

<1L/kg removed

>2L/kg unlikely

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

- Many drugs have 2 -3 compartment models;

  only 1st compartment concentration available for extracorporeal removal

Principles of drug removal

Volumes of distributions

Aciclovir 0.6L/kg

Cefotaxime 0.3L/kg

Colistin 0.34L/kg

Piperacillin 0.18L/kg

Vancomycin 0.7L/kg

Linezolid 0.6L/kg

Itraconazole 10L/kg

Moxifloxacin 2L/kg

Voriconazole 4.6L/kg

Midazolam 2.5L/kg

Amiodarone 6000L

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

Drug removal in AKI on RRT

Molecular size doesn't matter

Most drugs < 500 D (but protein binding matters)

Membrane cut - off: 20 - 50,000 D

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	✓

Factors affecting drug clearance on RRT

Additional system factors

- Filter type
- Continuous versus intermittent RRT
- Membrane interactions

  Adsorption of proteins on membrane

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

Drug dosing on RRT

Which dose ?

- Literature value
- Calculate
- Best guess
- Conduct study ?
- Refer to guidelines or protocol

Point of Prevalence Study

DALI

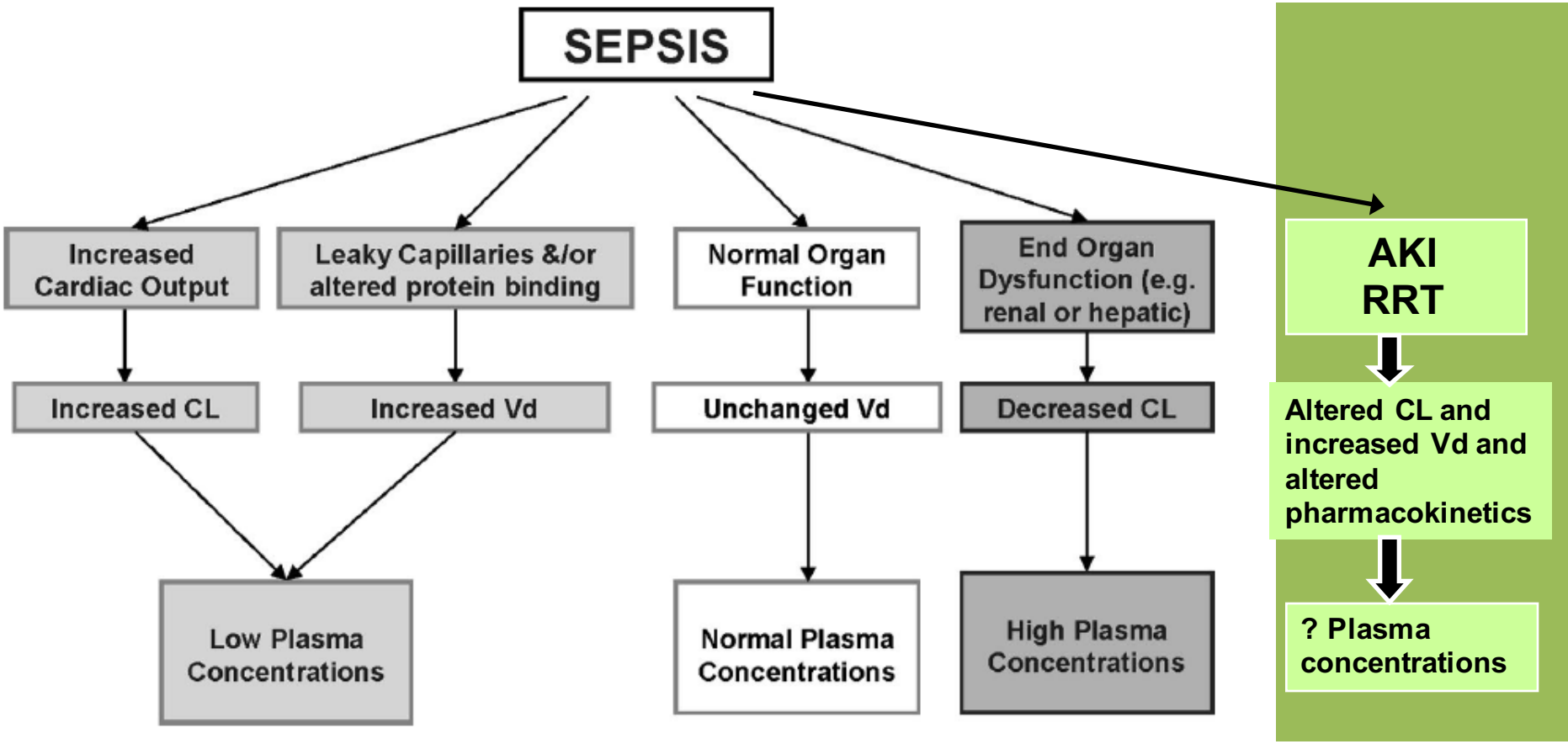
Defining Antibiotic Levels in Intensive care unit patients

Facts

- Morbidity and mortality for many infections in ICU is high
- Appropriate antibiotic therapy improves outcomes
- Relationship between antibiotic concentration and bacterial killing is well-defined for many antibiotics
- For ICU patients, the antibiotic concentration from a dose is poorly described

Variable drug levels in sepsis

ICU patients undergo pathophysiological changes leading to a wide possibility of drug concentrations from a single dose



DALI study

- **How frequently do critically ill patients achieve therapeutic antibiotic concentrations?**

DALI study

- **How frequently do critically ill patients achieve therapeutic antibiotic concentrations?**

Principle aim

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

DALI results

450 courses of antimicrobials measured

11.3% on RRT

Results:

Large proportion of patients were under- and over-dosed

PK variability high

Clear association between PK exposure and clinical outcome

Antibiotic dosing

Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: A multicentre pharmacokinetic study*

24 critically ill adult patients with AKI receiving ciprofloxacin, meropenem, piperacillin/tazobactam, or vancomycin during CRRT

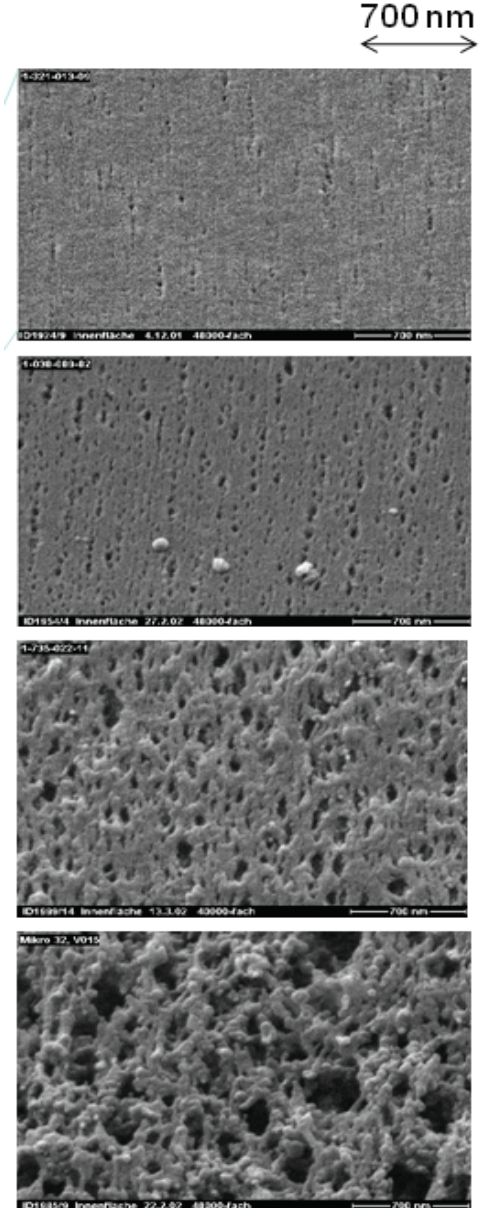
Conclusions:

- Significant variability in antibiotic trough concentrations
- Dosing of antibiotics failed to achieve the target trough antibiotic concentration during 25% of the dosing intervals.

DM Roberts et al. Crit Care Med 2012; 40: 1523–1528

Blood purification

Types of membranes



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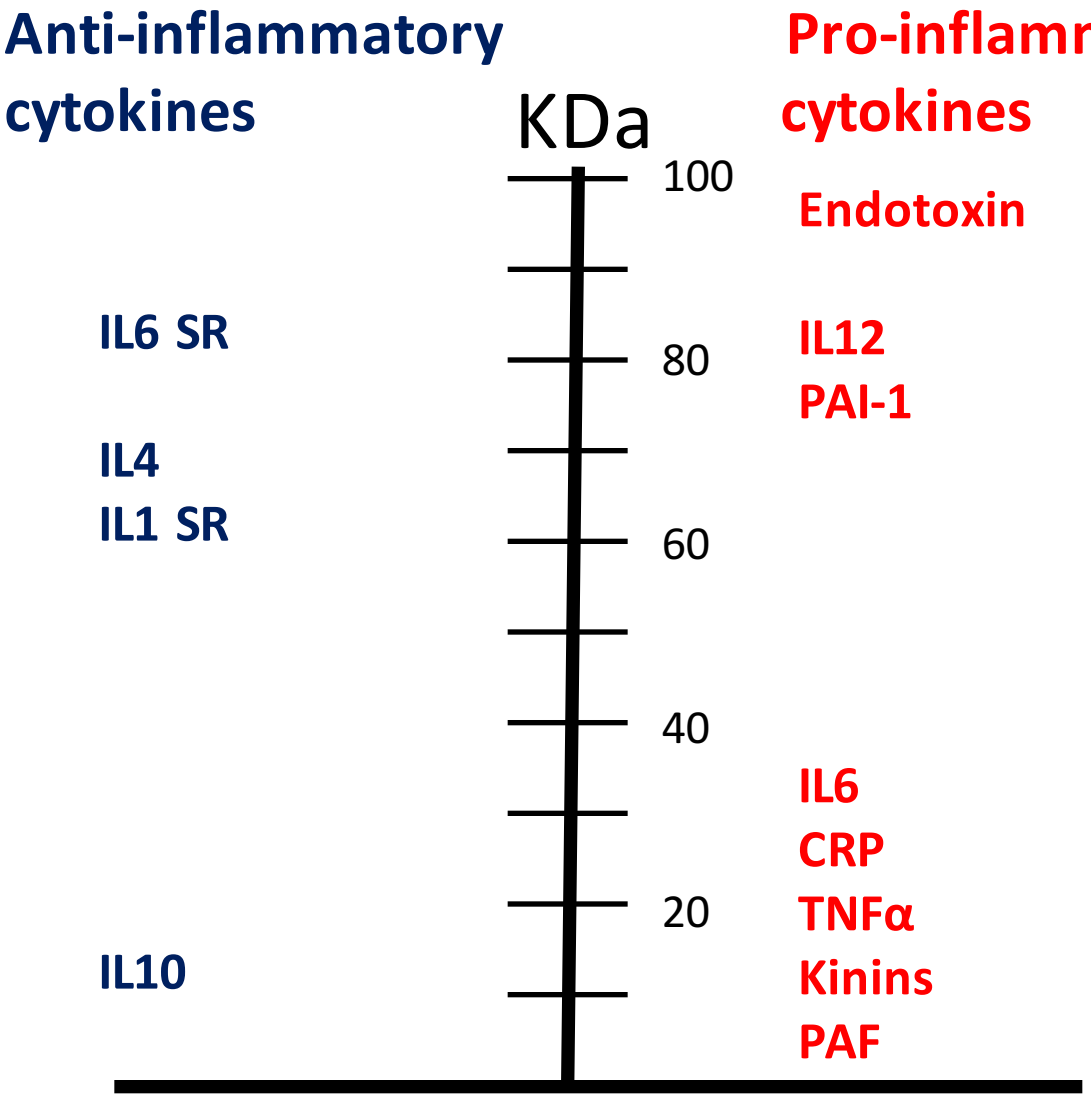
AKI and sepsis

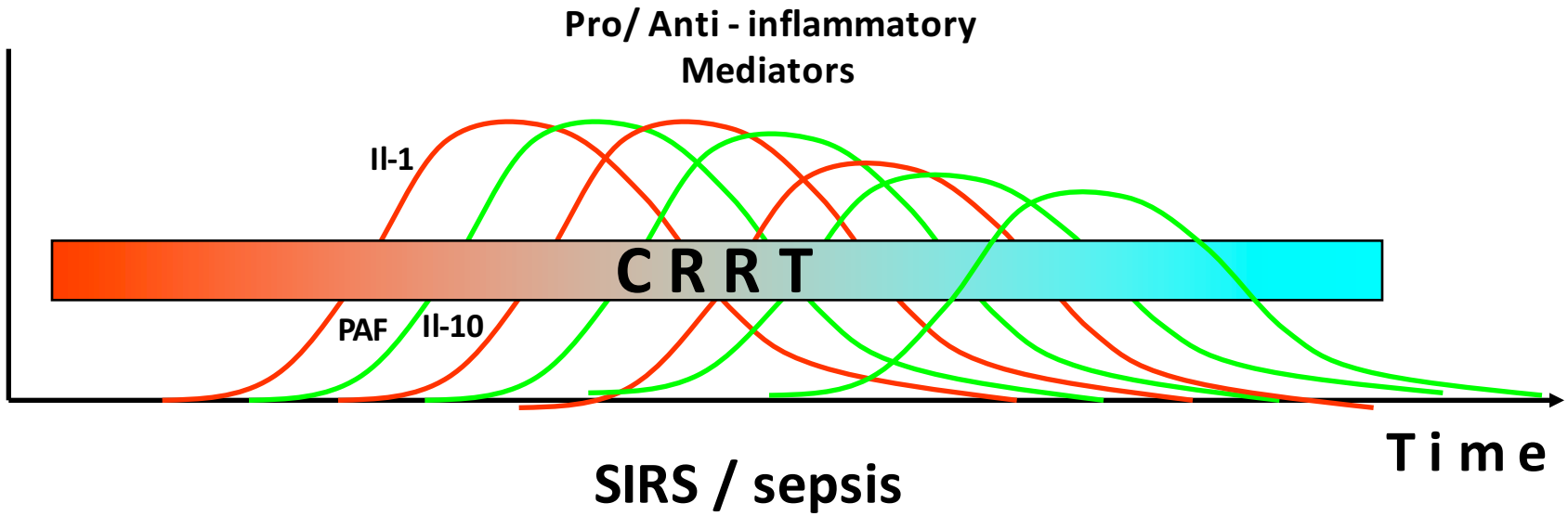


Membrane cut-off points

Polysulfone	30kDa
Polyamide	30kDa
AN69	50kDa
Polyamide100	100kDa

CRRT in sepsis

"Peak Concentration" Hyothesis



Blood purification in sepsis: Animal studies

Investigator	Model	No.	RRT	UF ml/kg/hr	Timing (related to sepsis)	Outcome
Gomez 1990	Dog/E Coli	8	CAVH	27	4 hrs	**↑ Cardiac Contractility**
Stein 1990	Pig/Endo	10	CAVH	20	Early	**↑Haemodynamics**
Grootendorst 1992	Pig/Endotoxin	6	CAVH	162	0	**↑ CO MAP**
Lee 1993	Piglet/Staph	6	CAVH	Up to 133	0	**Survival**
Mink 1995	Dog/EColi	10	CAVH	16	4 hrs	**↑CO DO_2**
Freeman 1995	Dog/EColi	7	CAVH	60	0	**No diff.**
Rogiers 1999	Dog/Endotoxin	5	CVVH	107/214	1 hr	**↑MAP**
Bellomo 2000	Dog/Endotoxin	8	CVVH	80	Pre	**↑MAP**
Yekebas 2001	Pig/Pancreatitis	12	CVVH	100	0	**↑Survival**

Blood purification in sepsis: Human studies

Investigator	Patients	AKI	No	Design	Type	UF ml/kg/hr	Outcome
Honore 2000	Septic shock	No	20	Observational	4 hrs	117	**Survival**
Cole 2002	Septic shock	No	24	RCT	Cont	27	**No effect**
Oudemans 1999	Septic shock	No	306	Observational	Cont	66	**Survival**
Bouman 2002	Septic shock	Yes	104	RCT	Cont	48	**No effect**
Joannes 2004	Septic shock	No	24	Observational	Cont	40-60	**Survival**
Laurent 2004	Post Arrest	No	61	RCT	Pulse 8hrs	200	**Survival**
Piccini 2006	Early septic shock	Yes	40	Historical Control	Pulse 6 hrs	45	**Survival**
Cornejio 2006	Septic shock	No	20	Observational	Pulse 12hrs	100	**Survival**
Merson 2006	Septic shock	No	45	Observational	Pulse 4 hrs	100	**Survival**

High dose RRT in sepsis / septic shock?

IVOIRE trial (HIgh VOlume in Intensive CaRE trial)

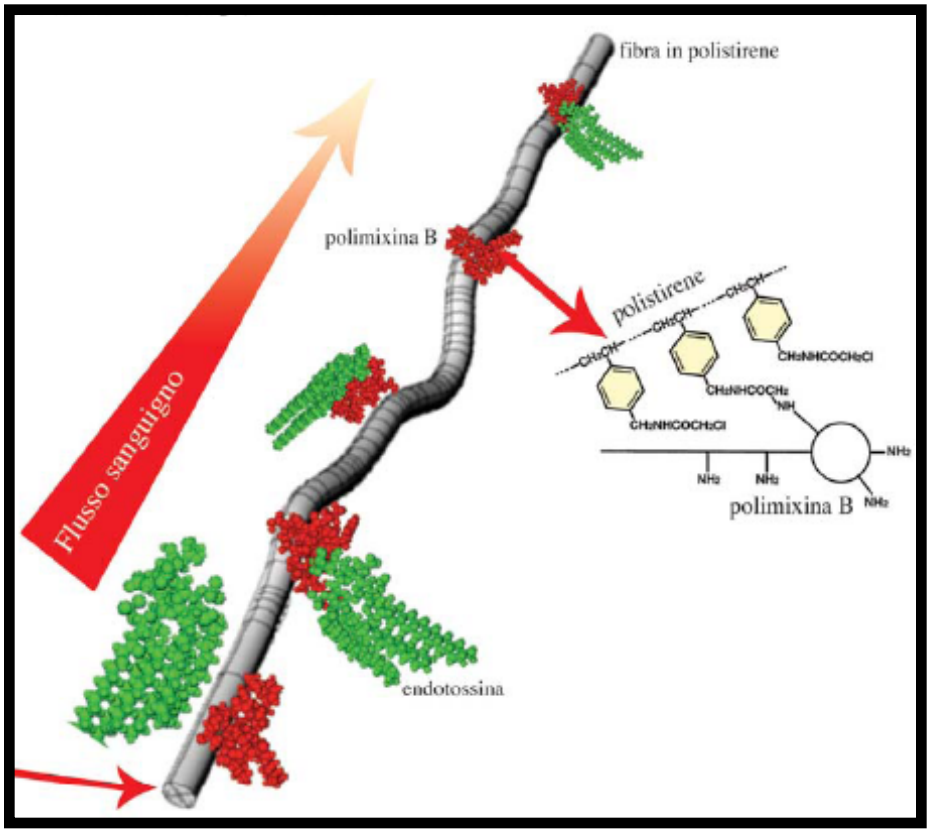
RCT: CVVH 70m/kg/hr vs CVVH 35ml/kg/hr
for 96 hrs

Planned study size: 460
Stopped in October 2010 after enrolment of 140 patients

Results: No difference in 28 day and 60 day mortality

Other techniques of blood purification

Coupling of filtration and absorption

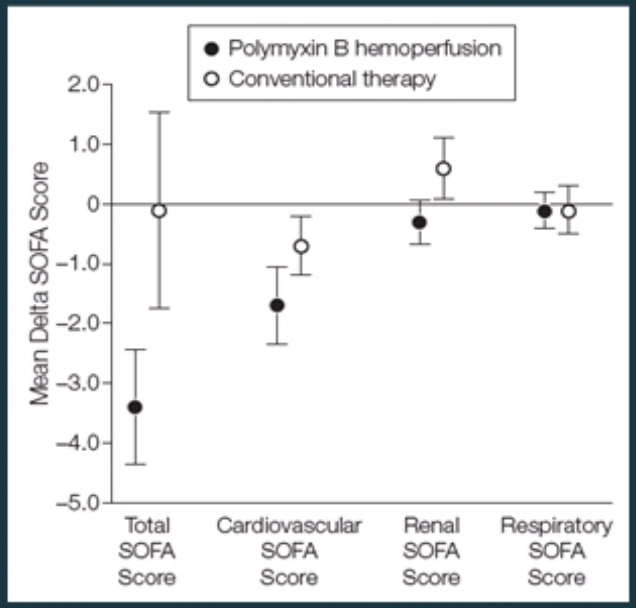


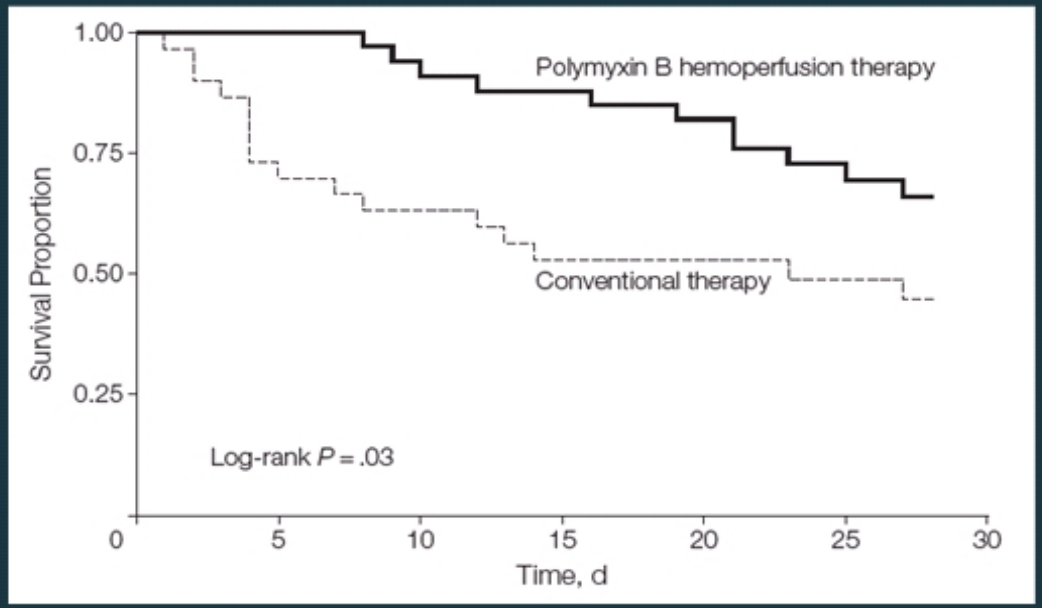
Polymyxin B-Immobilized Fiber (PMX-F) Column

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial

Physiological End Points	Polymyxin B Hemoperfusion Mean (95% CI) Baseline (n = 34)	Polymyxin B Hemoperfusion Mean (95% CI) 72 Hours (n = 34)	*P* Value	Conventional Therapy Mean (95% CI) Baseline (n = 30)	Conventional Therapy Mean (95% CI) 72 Hours (n = 27)	*P* Value
Mean arterial pressure, mm Hg	76 (72-80)	84 (80-88)	.001	74 (70-78)	77 (72-82)	.37
Inotropic score	29.9 (20.4-39.4)	6.8 (2.9-10.7)	<.001	28.6 (16.6-40.7)	22.4 (9.3-35.5)	.14
Vasopressor dependency index, $mm\ Hg^{-1}$	4.3 (2.7-5.9)	0.9 (0.3-1.5)	<.001	4.1 (2.3-6.0)	3.3 (1.3-5.3)	.26





Blood purification in sepsis

Blood Purification and Mortality in Sepsis: A Meta-analysis of Randomized Trials

Inclusion of studies: diagnosis of sepsis and comparison of blood purification techniques including hemofiltration, hemoperfusion, plasma exchange, or hemodialysis with no blood purification

Zhou F et al. Crit Care Med 2013, July 15

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16 trials, 827 patients

Conclusions:
Blood purification techniques were associated with lower mortality in patients with sepsis.
These results were mainly influenced by studies using polymyxin B hemoperfusion from Japan.

Zhou F et al. Crit Care Med 2013, July 15

Conclusions

- In critically ill patients, AKI and sepsis go hand-in-hand.
- Research suggests high variability in antibiotic levels in patients receiving RRT (risk of under- and overdosing)
- Recent data suggest that blood purification is effective in sepsis