Drug dosing in CRRT

Marlies Ostermann

Guy's and St Thomas' NHS
NHS Foundation Trust

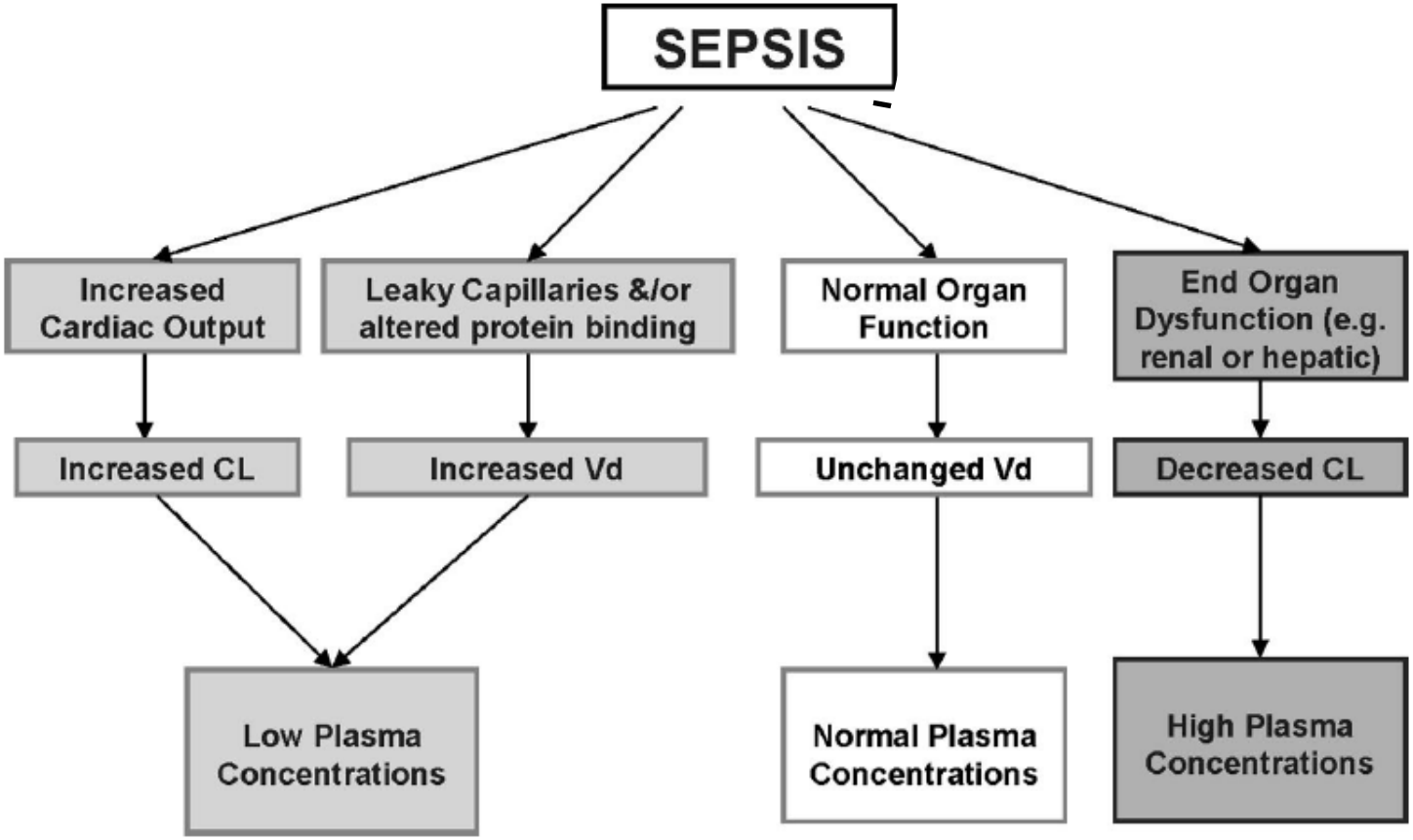
KING'S HEALTH PARTNERS

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

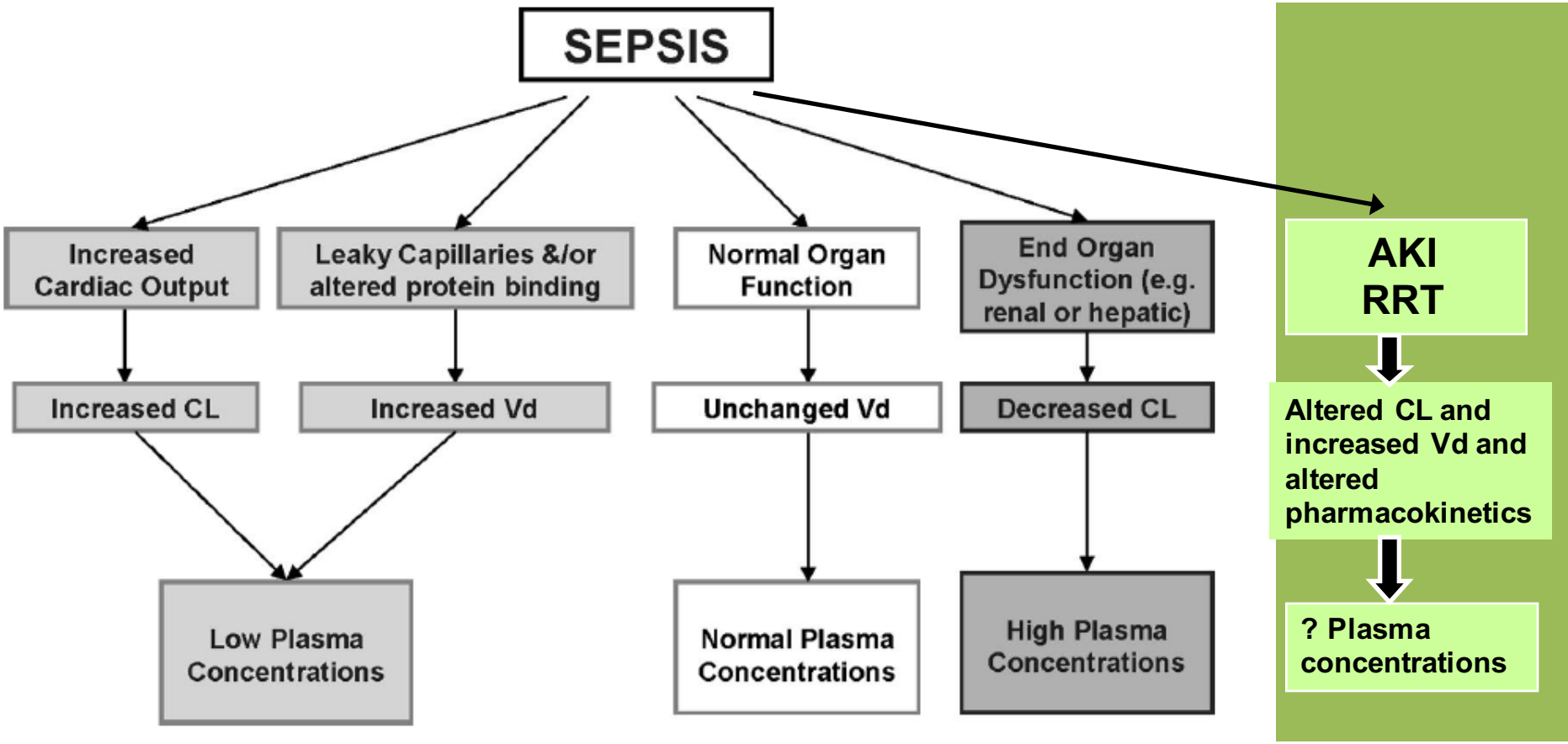
Variable drug levels in sepsis

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



Variable drug levels in sepsis

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



Principles of drug removal

Protein binding

- Most drugs < 500 D (unless protein bound)
- Only drugs not bound to plasma proteins will be removed by CRRT
- Some drugs bind to Albumin, glycoprotein and lipoprotein
- Drug-protein = 50,000 D

- Additional changes in ICU patients
  - pH
  - Albumin (↓)
  - bilirubin
  - polypharmacy (risk of drug interactions)

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 during RRT

- Difficult as PK alteration in critical illness

Drug factors:

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

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

Degree of protein binding matters!

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

  Unexpected interruptions
- Membrane interactions

  Adsorption of proteins on membrane

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

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

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

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

High proportion of patients with subtherapeutic antibiotic levels in high dose group

Solutions

1. Sampling of antibiotics in patients on RRT

Multicentre study
Actively recruiting

Will likely take another 2-3 yrs before results available.

2. Therapeutic drug monitoring

Very useful
Routine practice in some ICUs in Australia
Not affordable in NHS

Conclusions

- Drug dosing in AKI and RRT is very difficult
- Close collaboration with pharmacists is crucial