Medication Dosing in CRRT

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Learning Objectives

1. List the pharmacokinetic changes associated with AKI.
2. Determine the influence of CRRT on drug removal and dosing.
3. Review the effectiveness of current antimicrobial dosing in patients on CRRT.
4. Design effective strategies for dosing medications in patients receiving CRRT.

Background: Drug Dosing in **CRRT** is an **Art**, requiring a greater love of **Science**

- The Food and Drug Administration does not require pharmacokinetic (PK) studies of drugs in patients with AKI or those receiving CRRT
- PK studies in CRRT have been conducted < 20% of currently marketed drugs
  - Largely single center studies with varying CRRT modalities and patient populations.
- Drug dosing recommendations often come from extrapolation from CKD or ESRD patients.
  - AKI occurring in MOD has a different inflammatory milieu to CKD
  - Furthermore, time course of AKI is different with varying pharmacokinetics for the same drug over time
  - Attainment of target concentrations is challenging

Nolin T, et al. Clin J Am Soc Nephrol 2015; 10: 159–164.
Mueller BA, Smoyer WE. Clin Pharmacol Ther 2009; 86: 479–482.

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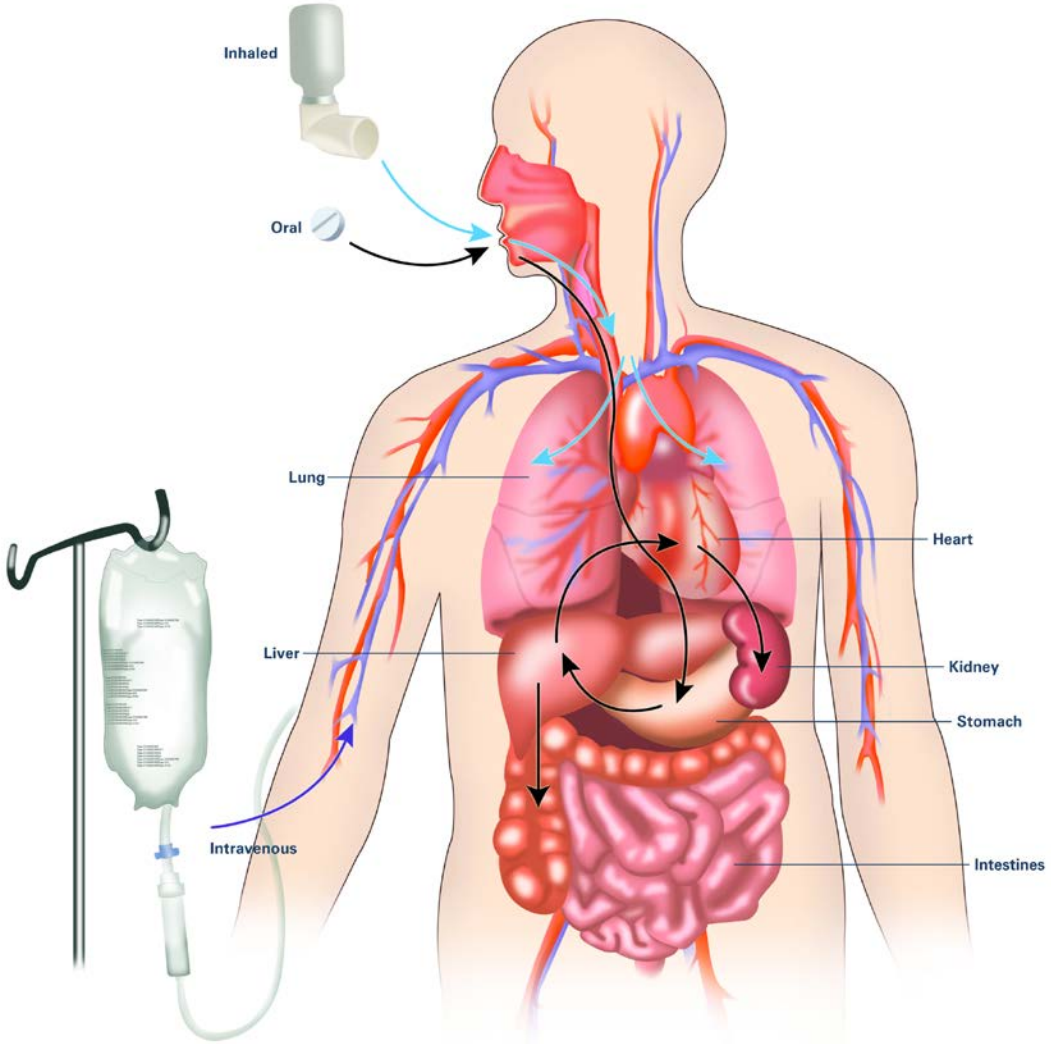
How Does AKI Alter the Pharmacokinetics of Drugs?



Absorption

Distribution

Metabolism

Elimination

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Critical Illness and AKI Alters Drug Absorption

- Changes in GI transit time
- Changes in gastric pH
  - Uremia or concurrent H2RA or PPIs
- Vomiting and diarrhea
- Gut dysmotility (edema, vasoconstrictors)
- Intestinal atrophy due to NPO status
- Decreased first-pass metabolism
- Decreased intestinal p-glycoprotein

Eyler, R. F. & Mueller, B. A. *Nat. Rev. Nephrol. 2011;* 7: 226–235

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Drug Distribution Changes During AKI

- Fluid overload may lead to increased ↑volume of distribution of hydrophilic drugs

Antibiotic	Healthy volunteers (l/kg)	Patients with AKI receiving RRT (l/kg)
Lipophilic drugs		
Ciprofloxacin	1.98[76]	1.60,[77] 1.65[78]
Levofloxacin	0.96,[79] 1.13[80]	1.02,[81] 1.51[82]
Hydrophilic drugs		
Amikacin	0.18[83]	0.44[84]
Daptomycin	0.10[85]	0.23[26]
Meropenem	0.17,[86] 0.18,[87] 0.27[88]	0.26,[89] 0.35,[28] 0.37[29]
Piperacillin	0.15[90]	0.14,[91] 0.18[92]
Vancomycin	0.39,[93] 0.59,[94] 0.63[95]	0.57,[96] 0.65[97]

- ↓Protein binding of drugs
  - Hypoalbuminemia and extracellular shifts
  - Uremia altering conformational binding of drugs to albumin

Eyler RF, Mueller BA. *Nat. Rev. Nephrol. 2011;* 7: 226–235

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Effect of AKI on Medication Clearance

- Reduction in CLcr corresponds with reduced clearance of drugs such as antimicrobials
- Sepsis may also alter tubular function but this has not been fully elucidated
- AKI also results in reductions in non-renal clearance but not always to the same extent as ESRD

Eyler RF, Mueller BA. *Nat. Rev. Nephrol. 2011;* 7: 226–235

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Non-renal clearance in AKI

The effect of AKI on the activity of selected rat model CYP enzymes

Rat CYP	Effect	AKI model
2A1	↔	Uranyl nitrate induced kidney injury
2B1/2	↔	Uranyl nitrate induced kidney injury
2C6	↔	Nephrectomy
	↔	Bilateral ureteral ligation
	↔	Glycerol-induced kidney injury
	↓	Cisplatin-induced kidney injury
2C11	↓	Uranyl nitrate induced kidney injury
2D2	↔	Nephrectomy
	↔	Bilateral ureteral ligation
	↔	Glycerol-induced kidney injury
	↔	Cisplatin-induced kidney injury
2E1	↑	Uranyl nitrate induced kidney injury
3A1 (3A23)	↑	Uranyl nitrate induced kidney injury
3A2	↓	Nephrectomy
	↔	Bilateral ureteral ligation
	↓	Glycerol-induced kidney injury
	↔	Cisplatin-induced kidney injury

Data from [24,25,75]. ↑, increase; ↓, decrease; ↔, no change; AKI, acute kidney injury; CYP, cytochrome P450.

Non-renal clearance data from humans

Drug	Normal Renal Function (mL/min)	AKI (mL/min)	ESRD (mL/min)
Imipenem	130	90-95	50
Meropenem	45-60	40-60	30-35
Vancomcyin	40	15	5

Villay et al. Crit Care 2008, **12:**235

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Renal Replacement Therapy May Improve Non-renal Clearance During AKI

- It is conceivable that removing potential toxins with RRT or plasma exchange may reverse AKI associated non-renal clearance changes

- ↑ Telithromycin concentration and exposure (as measured by area under the curve) in AKI approached that of healthy individuals within two hours of RRT

- 27% ↑activity in 14C-Erythromycin breath test (surrogate for CYP3A4 activity) observed 2h after initiation of RRT

Shi, J. *et al*. *J. Clin. Pharmacol.* 2004, *44*, 234–244.
Nolin, T.D. et al. *J. Am. Soc. Nephrol.* 2006, *17*, 2363–2367.

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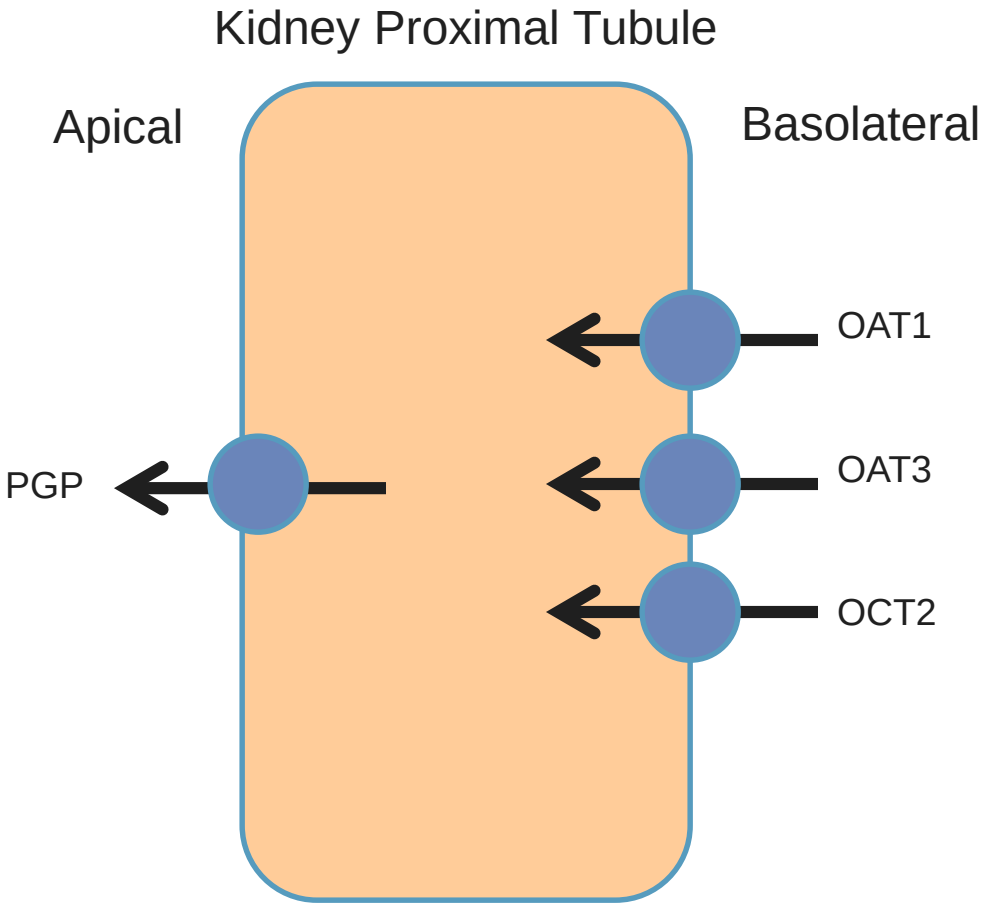
What About Drug Transport?

- Very little data on drug transporters
- Suppression of P-gp function during AKI
- Decreased OAT-1 and OAT-3 mRNA protein expression was observed in rats with AKI
- No data on OCT transport in AKI



Hagos Y et al. Toxins. 2010; **2**(8): 2055-82.
Robertson EE, Rankin GO. Pharmacology & Therapeutics 109 (2006) 399–412.
Burkhardt G. Pharmacology & Therapeutics. 2012;136:106–130
The International Transporter Consortium. Nat Rev Drug Discov. 2010; 9(3): 215–36

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Determinants of Drug Removal by CRRT

Drug Dependent Factors

- Protein Binding
- Volume of Distribution
- Molecular Weight
- Drug Charge (not clinically significant?)

Therapy Dependent Factors

- Type of CRRT modality
- Effluent flow rate
- Blood flow rate
- Fluid replacement (pre/post)
- Hemofilter (type and length of use)

Awdishu L, Bouchard J. How to Optimize Drug Delivery in Renal Replacement Therapy. Semin Dial. 2011 Mar-Apr;24(2):176-82.

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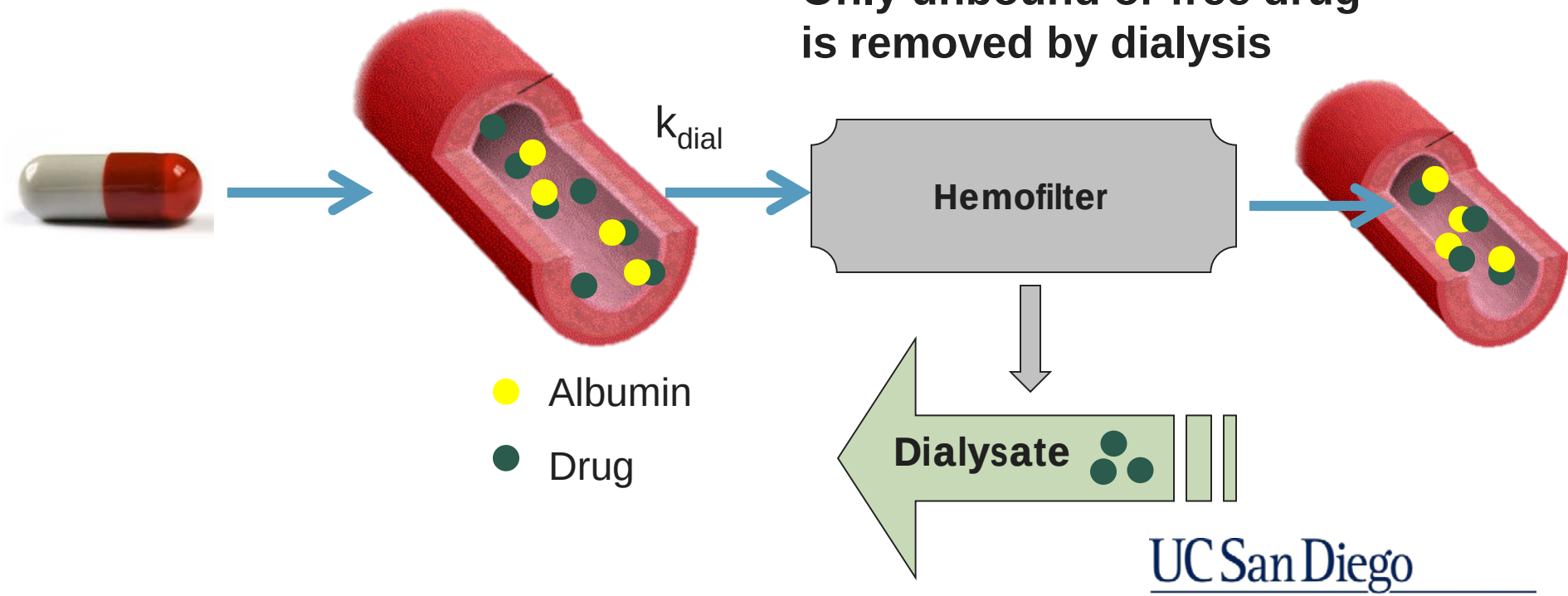
Protein Binding

Drugs with a high degree of protein binding (>90%) are less likely to be removed by dialysis

Only unbound or free drug is removed by dialysis



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Protein Binding

- Protein binding is the single most important determinant of drug removal by CRRT
- Protein binding > 90% indicates drug less likely to be removed by CRRT
  - Examples: ceftriaxone, warfarin
- Sieving coefficient (SC) measures the ability of a drug to convectively pass through the hemofilter
  - $SC_{measured} = [drug_{ultrafiltrate}]/[drug_{plasma}]$
  - $SC_{estimate} = 1\text{-}f_u$ (f_u = fraction unbound)

Awdishu L, Bouchard J. How to Optimize Drug Delivery in Renal Replacement Therapy. Semin Dial. 2011 Mar-Apr;24(2):176-82.

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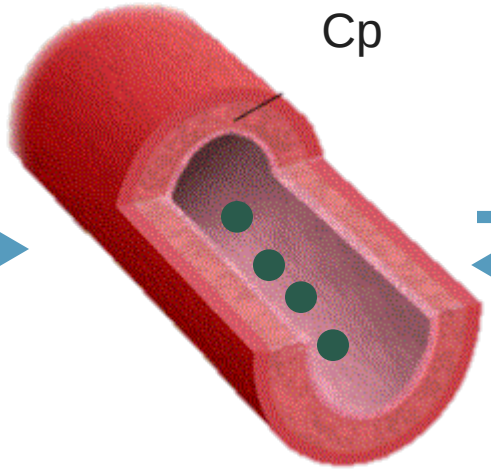
Volume of Distribution

Drugs with small Vd (< 0.3 L/kg)are located in the intravascular space and more likely to be removed by dialysis

Dose

Cp



k_{12}

k_{21}

Drugs with large Vd (> 1 L/kg) are likely distributed at other tissue sites

Rebound phenomenon is due to distribution of drug from tissue back to vascular space

k_{elim}

k_{dial}

Awdishu L, Bouchard J. How to Optimize Drug Delivery in Renal Replacement Therapy. Semin Dial. 2011 Mar-Apr;24(2):176-82.

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Molecular Weight

- Most drugs have a MW < 1500 daltons
- MW is not a major determinant of removal in CRRT since new hemofilters have large pore size

Drug	Molecular Weight Daltons or g/mol
Cefepime	480.6
Ceftazidime	547
Daptomycin	**1620**
Gentamicin	477.6
Meropenem	383.5
Piperacillin/tazobactam	539.5
Tobramycin	467.5
Vancomycin	**1450**

Principles of Medication Dosing in CRRT

- Estimation of renal function in AKI is very challenging given current biomarkers
  - Real time GFR measurements are being evaluated in clinical trials
- The sum of intrinsic renal CLcr and CRRT effluent rate normalized for drug protein binding provides a starting point
- When consulting drug databases, consider dose for equivalent CLcr CKD ≠ dose for equivalent CLcr CRRT
  - Changes in tubular secretion and reabsorption in CKD and ESRD are not the same in AKI with CRRT

Fissell W. Adv Chronic Kidney Dis. 2014; 20(1): 85-93

Estimating Clearance from RRT

Dialysis	Drug Clearance
$CVVH_{pre}$	CLcr ~ Effluent rate*SC* (Q_b/Q_b+Q_r)
$CVVH_{post}$ CVVHD CVVHDF	CLcr ~ Effluent rate*SC
IHD	CLcr < 10 mL/min
PD	CLcr < 10 mL/min

CLcr = creatinine clearance estimate
$CVVH_{pre}$ = pre-filter replacement fluid
$CVVH_{post}$ = post filter replacement fluid
IHD = intermittent hemodialysis
Q_b = blood flow rate
Q_r = replacement fluid rate
SC = sieving coefficient

Convert effluent rate to mL/min for CLcr estimate

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Principles of Medication Dosing in CRRT

- Evaluate primary literature for drug dosing studies
  - Ensure the CL provided by modality is the same as your institution protocol
  - Dose delivered ≠ dose prescribed (use effluent rate not prescribed UF + dialysate rates)
- When available, TDM should be used, especially for drugs with narrow TI.
- CL of some drugs correlates very closely with CLcr
  - Aminoglycosides
  - Vancomycin
- Consider mechanism of action of the drug and pharmacodynamic evaluation of therapy ie. AUC/MIC ratios for the pathogen targeted

Awdishu L, Bouchard J. How to Optimize Drug Delivery in Renal Replacement Therapy. Semin Dial. 2011 Mar-Apr;24(2):176-82.

Killing Properties of Different Anti-infectives

Antibiotic	Pharmacodynamic Profile	Target
Aminoglycosides	Concentration-dependent	AUC/MIC Peak:MIC
Colistin	Concentration-dependent	AUC/MIC
Daptomycin	Concentration-dependent	AUC/MIC
Fluoroquinolones	Concentration-dependent	AUC/MIC Peak:MIC
Carbapenems	Time-dependent	%time above MIC
Cephalosporins	Time-dependent	%time above MIC
Linezolid	Time-dependent	AUC/MIC
Penicillins	Time-dependent	%time above MIC
Vancomycin	Time-dependent	AUC/MIC

Awdishu L, Bouchard J. How to Optimize Drug Delivery in Renal Replacement Therapy. Semin Dial. 2011 Mar-Apr;24(2):176-82.
Eyler RF, Mueller BA. *Nat. Rev. Nephrol. 2011;* 7: 226–235

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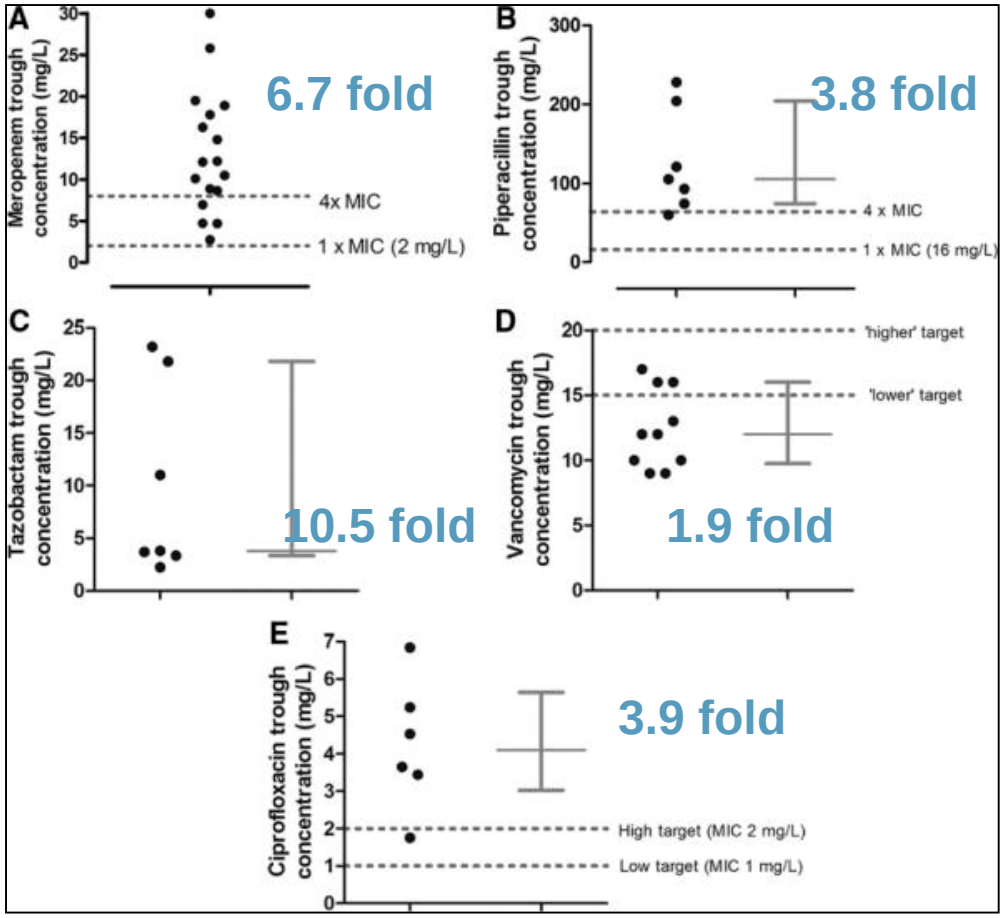
Antibiotic Exposure Variability from RENAL study



Antibiotic and Number of Samples	Lower Therapeutic Target[a] (%)	Higher Therapeutic Target[b] (%)
Meropenem (n = 17)	100	76
Piperacillin (n = 7)	100	86
Vancomycin (n = 10)	30	0
Ciprofloxacin (n = 6)	100	83

15% dosing intervals (n = 40) did not achieve the antibiotic therapeutic targets

40% did not achieve the higher target concentrations

10% were excessive in dosing

Wide variability in observed trough concentrations for each antibiotic

Roberts JA et al. Critical Care Medicine. 2012; 40(5):1523-1528.

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Does CRRT Dose Intensity Affect Pharmacokinetics?

Antibiotic (Abx)	Abx CL Mean ± SD CVVHDF 25 mL/kg/hr	Abx CL Mean ± SD CVVHDF 40 mL/kg/hr	P value
Ciprofloxacin	17 ± 3	19 ± 8	0.5139
Meropenem	21 ± 9	23 ± 13	0.4802
Piperacillin	26 ± 12	25 ± 10	0.9091
Tazobactam	53 ± 24	38 ± 13	0.0642
Vancomycin	22 ± 5	28 ± 7	<0.0001

Roberts DM et al. Crit Care 2015; 19:84

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Vancomycin Dosing and Achievement of Target Concentrations

Regimen	Predicted Certainty (%)			
	Trough 15–20 mg/L	Trough < 12 mg/L	Trough > 25 mg/L	AUC_{24h}/MIC ≥ 400*
1 g q24h	12	51	19	52
1.25 g q24h	13	41	27	63
1.5 g q24h	13	34	35	71
1.75 g q24h	12	28	42	78
2.0 g q24h	11	24	48	83
15 mg/kg q24h	12	43	26	71
10 mg/kg q24h	10	60	14	41

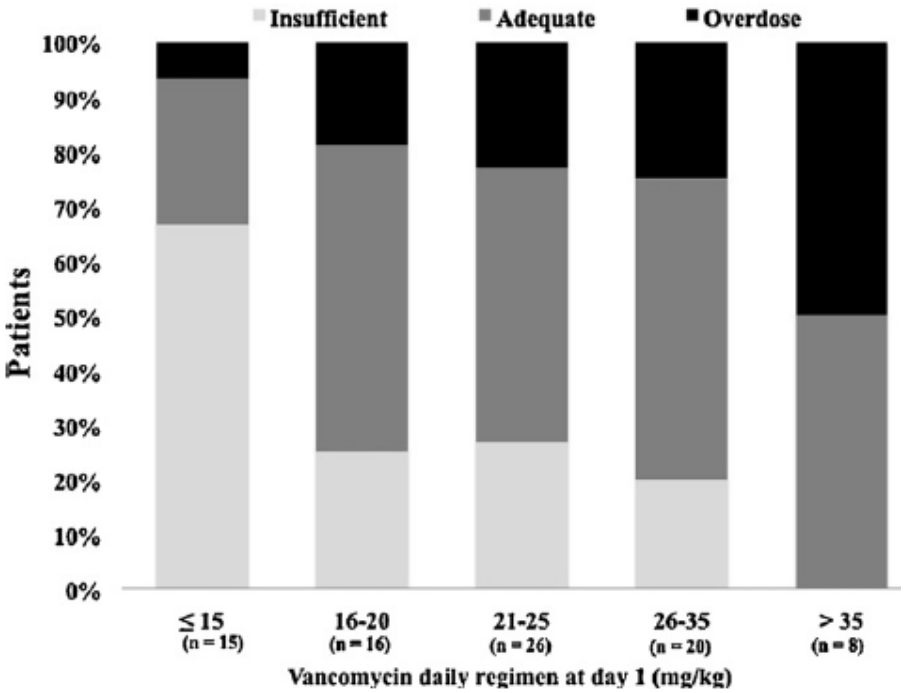
AUC_{24h} = area under the concentration–time curve over 24 h, MIC = minimum inhibitory concentration.
MIC was assumed to have a normal distribution, with a range between 0.5 and 2 mg/L and a mean value of 1 mg/L, with 1 million iterations using Monte Carlo simulation.

van de Vijsel LM et al. Can J Hosp Pharm. 2010 May-Jun; 63(3): 196–206.

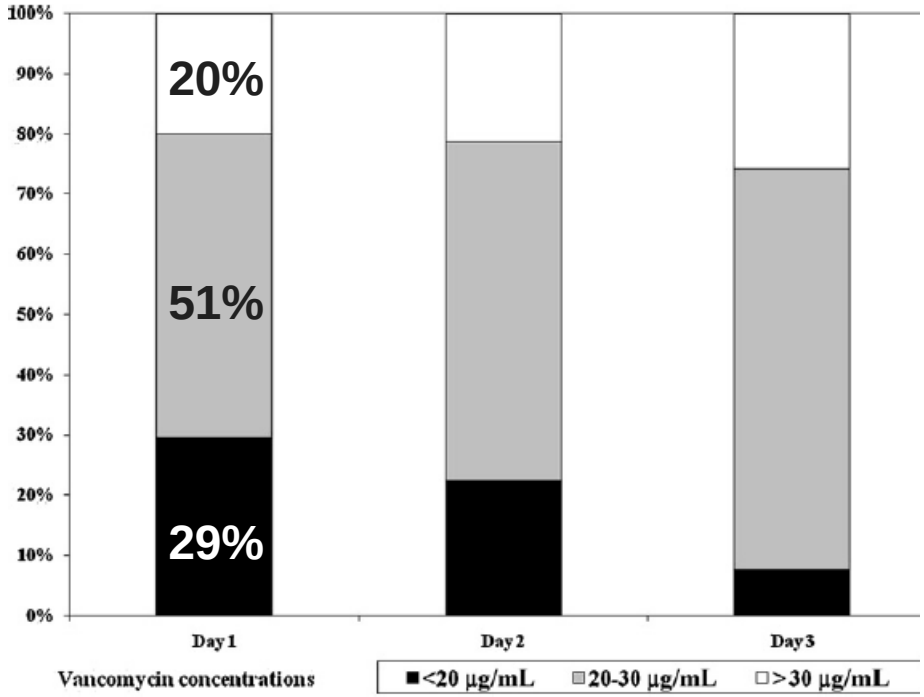
Continuous Infusion Vancomycin

N=85

Mean D1 Dose 16.4±6.4 (LD), 23.5±8.1



24.7±9.0 **26.0±8.1** **27.7±9.3**



Covajes C et al. Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy. Int J Antimicrob Agents. 2013 Mar;41(3):261-6.

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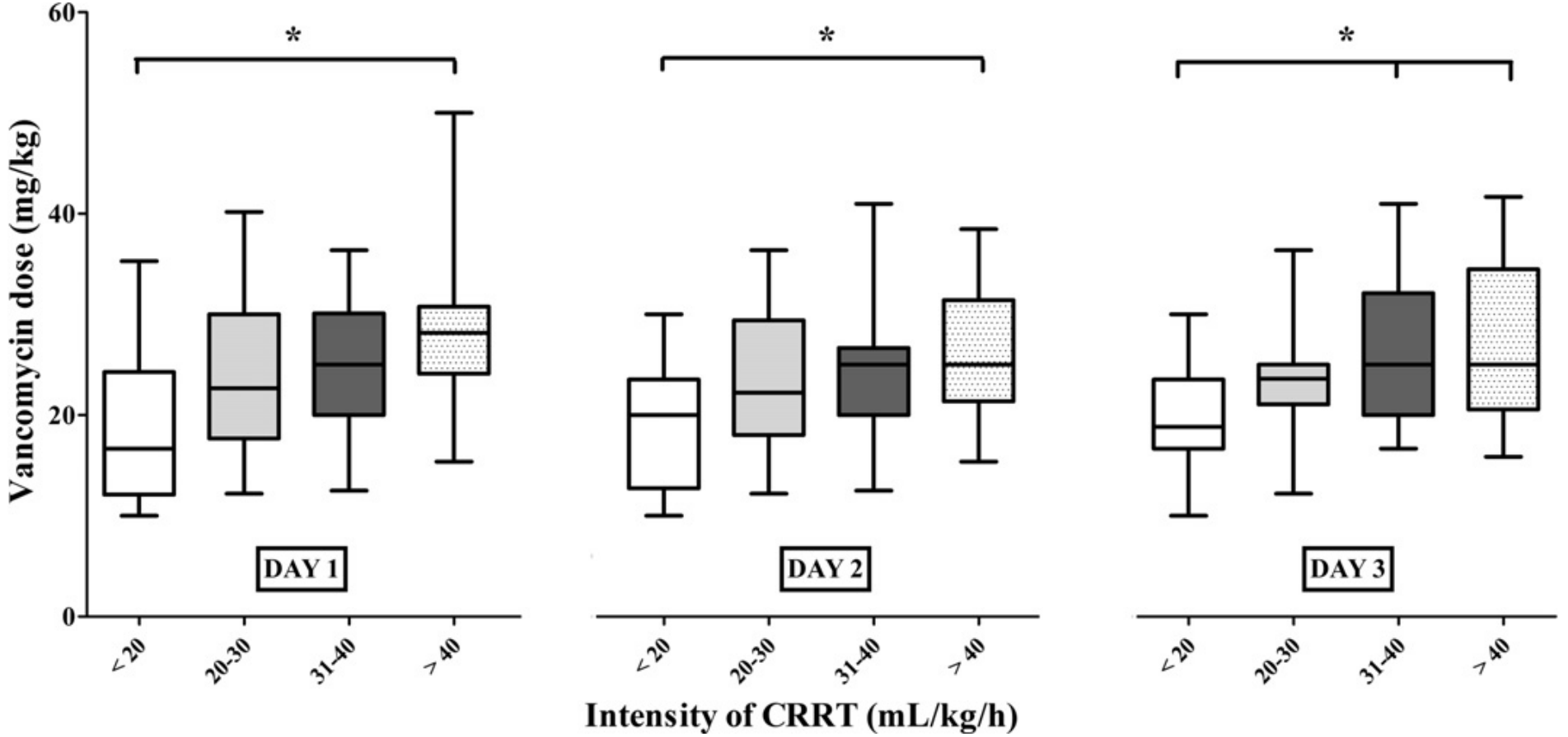
Vancomycin Concentration/Dose By CRRT Dose



The intensity of CRRT influenced vancomycin dosing D1-3 and concentrations on Day 1 of therapy.

Covajes C et al. Int J Antimicrob Agents. 2013 Mar;41(3):261-6.

Piperacillin/Tazobactam PK in CRRT

	Total Drug	Free Drug
Piperacillin PK parameters		
protein binding (%)	19.0±9.7	
Vd (L)	34.5 (30.5)	38.2 (26.5)
Vd (L/kg)	0.38 (0.20)	0.43 (0.26)
ke (h^{-1})	0.104 (0.052)	0.120 (0.073)
$t_{1/2}$ (hours)	9.6 (4.2)	5.8 (3.6)
clearance (ml/min)	64.5 (59.7)	78.6 (62.2)
CRRT clearance (ml/min)	27.6 (15.2)	33.2 (14.9)
Tazobactam PK parameters		
protein binding (%)	14.6 (36.5)	
Vd (L)	38.1 (27.6)	50.6 (54.1)
Vd (L/kg)	0.38 (0.33)	0.50 (0.56)
ke (h^{-1})	0.086 (0.058)	0.089 (0.063)
$t_{1/2}$ (hours)	11.5 (9.4)	7.8 (6.3)
clearance (ml/min)	48.3 (46.5)	83.6 (86.5)
CRRT clearance (ml/min)	25.7 (15.3)	35.7 (17.8)

	Piperacillin		Tazobactam	
	Total	Free	Total	Free
Peak	135 (78.4)	115 (62.1)	20.9 (16.2)	16.3 (16.4)
Trough	66.2 (39.3)	54.8 (35.2)	11.7 (9.7)	9.0 (12.6)
fT>MIC=64 µg/ml>50%	83%	77%		

2.25-3.375 g IV q6-12h over 30 min

Bauer S, Charbel S, Connor MJ et al. Pharmacokinetics and Pharmacodynamics of Piperacillin-Tazobactam in 42 Patients Treated with Concomitant CRRT. CJASN 2012; 7(3):452-7.

Extended Infusion Piperacillin-Tazobactam in Critically Ill Patients Receiving CVVHDF

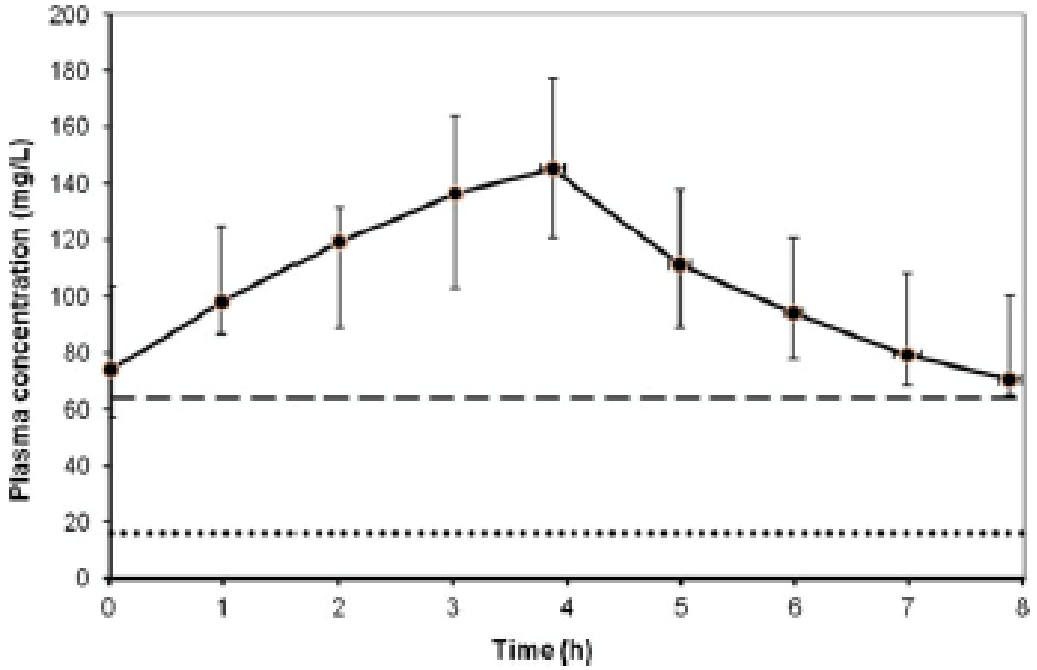


Figure 1. Unbound piperacillin plasma concentration over time. Data are presented as median (interquartile Q1, Q3). Dashed line: MIC90 of *Pseudomonas aeruginosa* (64 mg/L). Dotted line: Susceptibility breakpoint of *Pseudomonas aeruginosa* (16 mg/L).

4.5 g IV q8h given as 4 hour infusion

90% patients achieved 50% time above MIC_{90}

Awisi D, et al. Pharmacotherapy 2015;35(6): 600-607.

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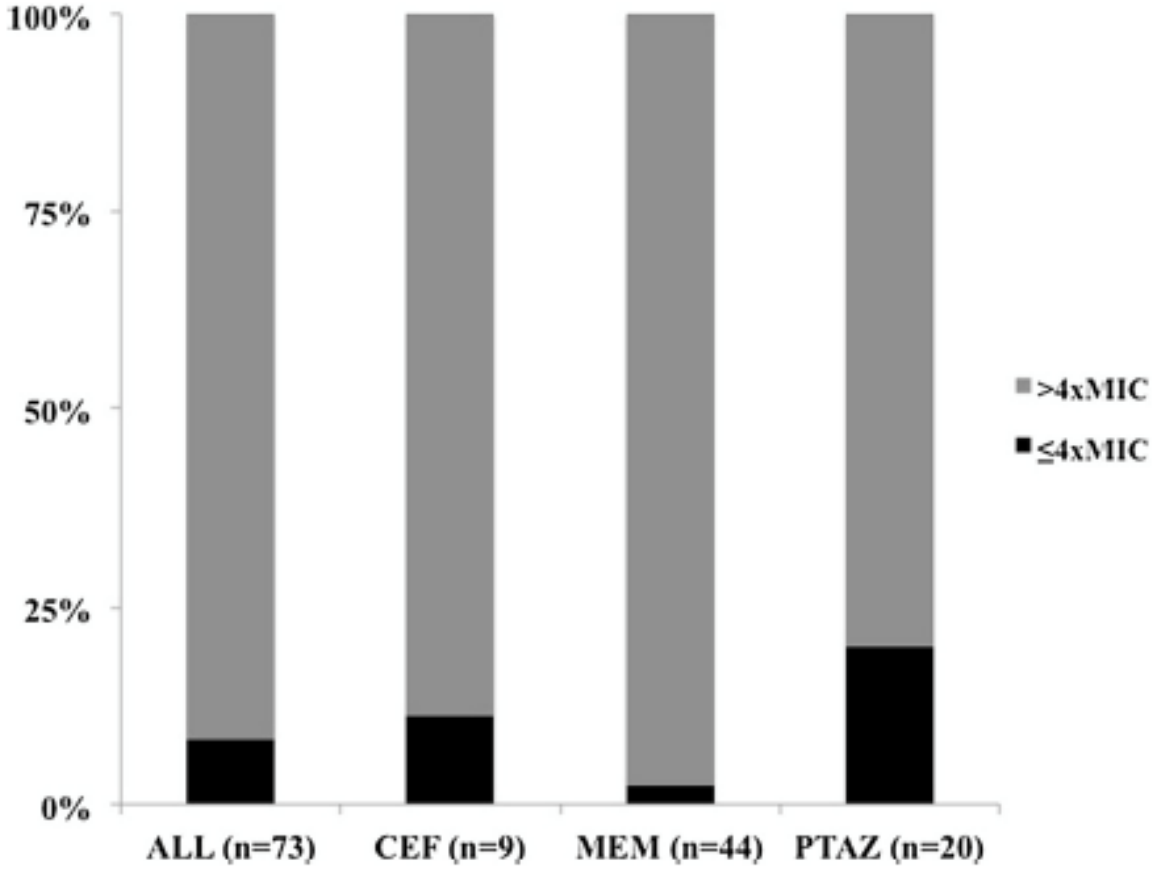
Beta Lactam Concentrations above MIC_{90} for Pseudomonas



CEF= ceftazidime or cefepime 2 g q8h
MEM = meropenem 1 g q8h
PTAZ = piperacillin/tazobactam 4 g q8h

Beumier et al. Crit Care 2014

Therapeutic targets achieved in 90% patients overall

>50% samples with excessive concentrations

Time > 4 x MIC weakly correlated with CRRT dosing intensity

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TDM for Beta Lactam Dosing

Antibiotic	Standard initiation dose	TDM samples	Dose maintained	Dose increased[a]	Dose decreased[b]
TZP	4.5 g q6h	9	2 (22%)	1 (11%)	6 (67%)
	4.5 g q8h	37	29 (78%)	–	8 (22%)
	4.5 g q12h	7	4 (57%)	2 (29%)	1 (14%)
Ampicillin	1 g q6h	1	–	–	1 (100%)
Meropenem	0.5 g q6h	5	5 (100%)	–	–
	0.5 g q8h	17	13 (76%)	1 (6%)	3 (18%)
	0.5 g q12h	1	–	1 (100%)	–
	1 g q6h	2	1 (50%)	1 (50%)	–
	1 g q8h	10	5 (50%)	2 (20%)	3 (30%)
	1 g q12h	3	1 (33%)	1 (33%)	1 (33%)
Penicillin G	1.2 g q4h	1	–	–	1 (100%)
	1.8 g q4h	2	–	1 (50%)	1 (50%)
	1.8 g q6h	2	1 (50%)	–	1 (50%)
Flucloxacillin	1 g q4h	1	–	1 (100%)	–
	1 g q8h	1	–	1 (100%)	–
	2 g q6h	7	7 (100%)	–	–
Ceftriaxone	1 g q12h	4	4 (100%)	–	–
	2 g q12h	1			1 (100%)
Total		111	72 (65%)	12 (11%)	27 (24%)

TZP, piperacillin/tazobactam; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q4h, every 4 h.

[a] Includes increased dosing frequency or increased dose.

[b] Dose adjustment for TZP was based on piperacillin concentrations only.

Economou C et al. Int J Antimicrob Agents 2017.

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Fluconazole

Patient no.	Dose (mg/day)	C_{max} (µg/ml)	C_{24h} (µg/ml)	C_{min} (µg/ml)	AUC_P (µg h/ml)	AUC_F (µg h/ml)	S	Cl_T (ml/min)	Cl_{EC} (ml/min)	$t_{1/2}$ (h)	V_{SS} (l/kgBW)
CVVHD											
1	400	10.7	6.7	3.8	160.1	134.4	0.84	38.1	30.5	14.8	0.65
2	400	12.7	10.0	6.9	240.7	130.0	0.54	31.2	18.6	26.0	1.28
3	400	11.8	7.7	5.7	184.6	159.8	0.87	33.2	29.9	23.6	0.97
4	600	10.6	5.9	4.1	142.2	125.8	0.88	43.8	32.2	25.1	1.15
5	800	16.9	13.5	11.2	324.9	303.0	0.93	41.1	33.1	35.1	0.76
6	800	22.2	14.2	8.8	340.0	339.7	1.00	40.1	38.7	18.3	1.06
CVVH											
1	400	11.9	8.1	6.2	195.2	173.0	0.89	21.5	17.3	29.8	0.74
2	400	12.8	10.3	7.5	247.5	137.9	0.56	19.0	10.2	41.3	1.23
3	400	11.3	8.8	7.2	211.0	176.9	0.84	19.5	15.3	51.6	1.24
4	600	14.1	7.3	8.0	223.0	228.0	1.02	31.7	20.2	24.0	0.79
5	800	17.9	14.1	12.1	339.5	346.5	1.02	36.5	19.3	39.6	0.76
6	800	24.0	16.5	11.8	396.3	406.0	1.02	23.8	22.6	28.3	0.97

For life threatening candida infections, target trough 10-12, peak 28 mcg/mL

Fluconazole undergoes tubular reabsorption in normal renal function. In AKI on CRRT, tubular reabsorption of fluconazole is reduced resulting in the need for higher doses than in normal renal function.

Muhl E et al. Eur J Clin Pharmacol. 2000; 56: 671-8.
Pittrow and Penk. Mycoses. 1999;42:17-19.

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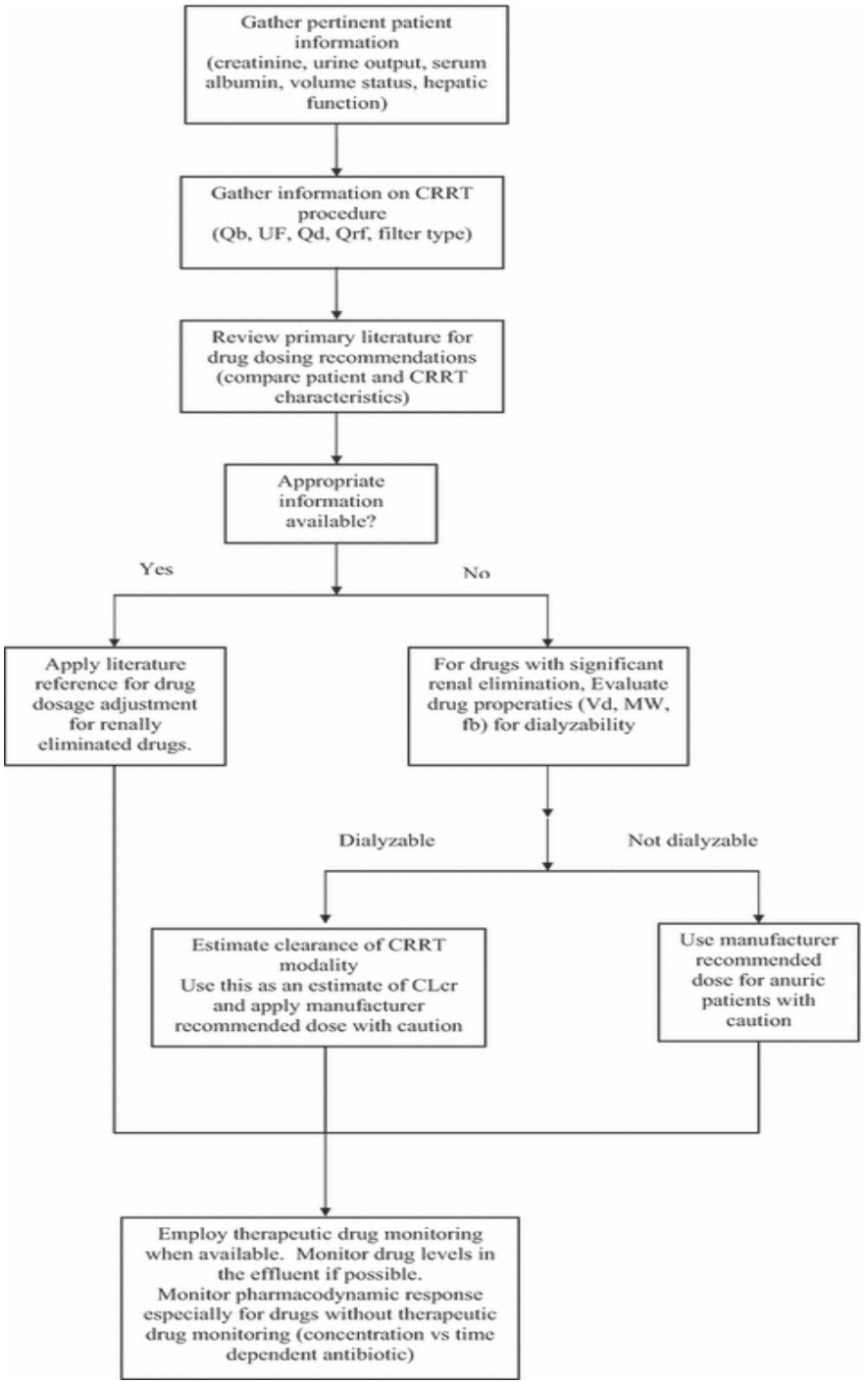
Excerpt from UCSD CVVHDF Dosing Card

DRUG	INDICATION	DOSE	COMMENTS
CEFAZOLIN	Sepsis or Pneumonia	2 g IV q 12 h	
CEFEPIME	Sepsis or Pneumonia	1 g IV q 12 h	
CEFEPIME	MDR GNR*, Pseudomonas aeruginosa	2 g IV q 12 h	
CEFTAZIDIME	Sepsis	1 g IV q 12 h	
CEFTAZIDIME	Pneumonia	2 g IV q 12 h	
CIPROFLOXACIN AdjWt	Sepsis or Pneumonia	200 mg IV q 8-12 h	
DAPTOMYCIN TBW	SSSI, Bacteremia or Endocarditis	4-8 mg/kg q 48 h	
FLUCONAZOLE TBW	Sepsis or Pneumonia	400-800 mg IV q 24 h	400 mg for sensitive Candida species, 800 mg for kruseii or glabrata
MEROPENEM	Sepsis	1000 mg IV q 12 h	
MEROPENEM	Pneumonia	1000 mg IV q 8 h	
PIPERACILLIN/TAZOBACTAM	Sepsis or Pneumonia	3.375 g q 8 h	Extended Infusion over 4 hrs
PIPERACILLIN/TAZOBACTAM	MDR GNR*, Pseudomonas aeruginosa	4.5 g q 8 h	Extended Infusion over 4 hrs
VANCOMYCIN AdjWt	Sepsis or Pneumonia	20 mg/kg load, 15 mg/kg q 24 h	Check serum concentrations 2h post first dose and random day 3 am

Awdishu L, James C. Department of Pharmacy Dosage Guidelines for Adult Patients on CVVHDF. 2017 Draft.

How to Optimize Drug Delivery in Renal Replacement Therapy



Awdishu L, Bouchard J. Sem Dial. 2011;24(2): 176-82.

Drug Dosing Pearls for Patients with AKI Receiving CRRT

- ☑ Utilize intravenous drug administration to bypass absorption issues
- ☑ Adjust the loading dose of hydrophilic drugs to account for increased Vd
- ☑ Consider pharmacodynamic properties for drug when making adjustments to dosing intervals
- ☑ Look for primary literature if available
- ☑ Employ TDM frequently
- ☑ PK parameters vary day by day, as UOP recovers or fluid status changes, drug dosing should be reassessed

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Eyler, RF & Mueller BA. *Nat. Rev. Nephrol*. 2011; 7: 226–235

Kidney Health Initiative

Pharmacokinetic Assessment in Patients Receiving Continuous RRT: Perspectives from the Kidney Health Initiative

Thomas D. Nolin, George R. Aronoff, William H. Fissell, Lokesh Jain, Rajnikanth Madabushi, Kellie Reynolds, Lei Zhang, Shiew Mei Huang, Rajnish Mehrotra, Michael F. Flessner, John K. Leypoldt, Jennifer W. Witcher, Issam Zineh, Patrick Archdeacon, Prabir Roy-Chaudhury, and Stuart L. Goldstein

https://www.asn-online.org/khi/project-pharmacokinetics.aspx

Nolin T, et al. Clin J Am Soc Nephrol 2015; 10: 159–164.

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