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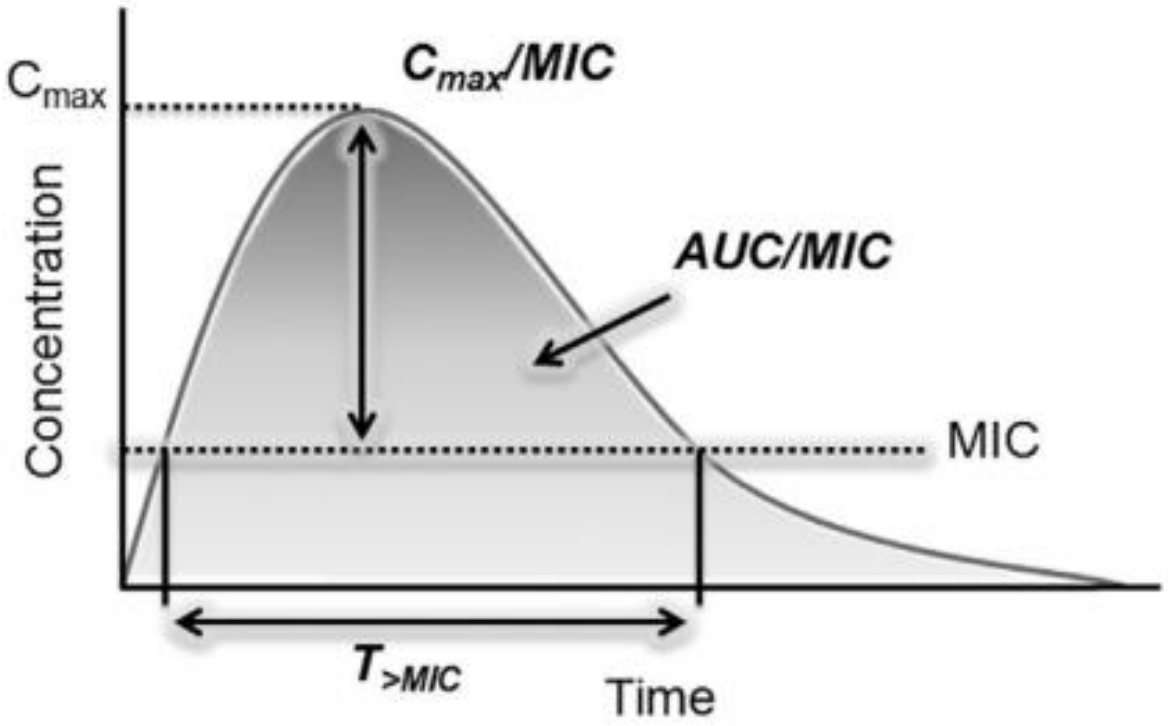
Antibiotic Dosing in Special Populations

October 9, 2019

Background

- Antibiotics are commonly prescribed in the ICU
- Challenges to finding a dose that's just right
- Particular challenges
  - Critical illness
  - Obesity
  - Continuous Renal Replacement Therapy (CRRT)

Antimicrobial PK-PD and Efficacy



3 primary PK-PD predictors of efficacy:

Time>MIC
Cmax:MIC
AUC:MIC

β-lactam Pharmacodynamics

- Goal of therapy: To optimize ß-lactam exposure (time above MIC) for optimal bactericidal activity

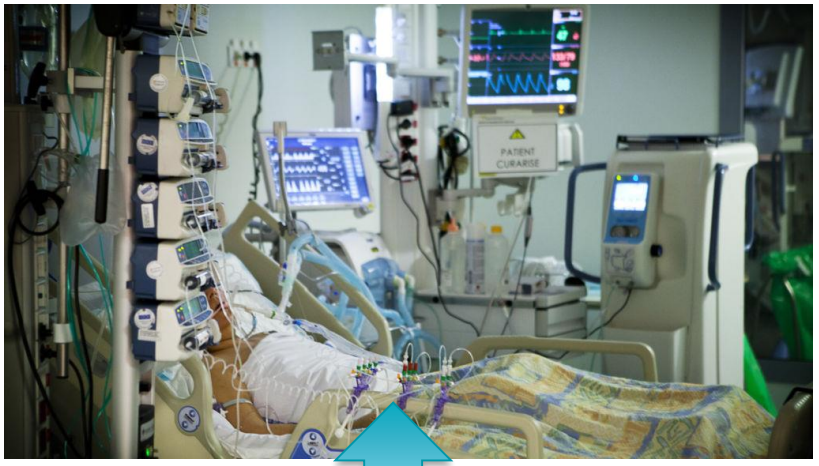
- Required unbound % T>MIC for cidal kill:
  - **60-70%** of dosing interval – cephalosporins
  - **50%** of dosing interval – penicillins
  - **40%** of dosing interval - carbapenems

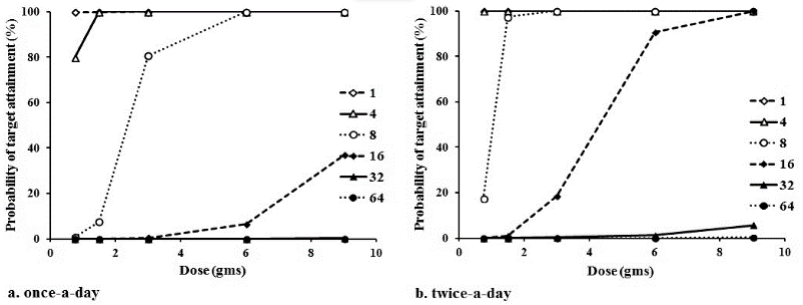
Plasma concentrations are usually surrogates

"Adequate" concentrations in the serum

"Adequate" concentrations at the site of infection

Where have our antibiotic doses come from?





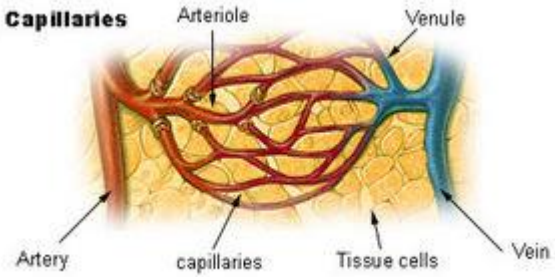
Pertinent Antibiotic Characteristics

	Hydrophilic Antibiotics	Lipophilic Antibiotics
Pharmacokinetic Characteristics	• Lower volume of distribution • Predominantly renally cleared • Low intracellular penetration	• Higher volume of distribution • Predominantly hepatically cleated • Good intracellular penetration
Examples	• Beta-lactams • Aminoglycosides • Glycopeptides • Linezolid • Colistin	• Fluoroquinolones • Macrolides • Lincosamides • Tigecycline

Critically Ill Patients

- Impaired absorption
  - Decreased peak and AUC

- Capillary leak
  - Increased Vd
  - Decreased plasma concentrations
  - Delayed distribution (stasis of fluid in tissues)



Critically Ill Patients

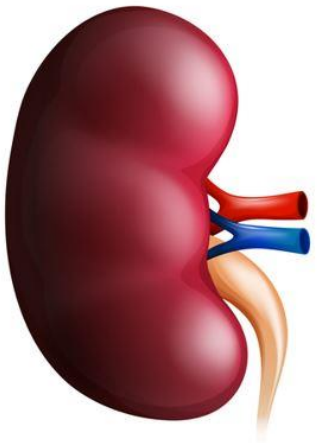
- Impaired absorption
  - Decreased peak and AUC

- Capillary leak
  - Increased Vd
  - Decreased plasma concentrations
  - Delayed distribution (stasis of fluid in tissues)

- End-organ damage
  - Decreased clearance
  - Increased AUC

- Hypoalbuminemia
  - Increased free fraction, variable effects

- Augmented clearance – decreased AUC



Augmented Renal Clearance

- Variable definitions exist
  - GFR > 160 mL/min/1.73m2 in men
  - GFR >150 mL/min/1.73m2 in women

- Caused by a variety of factors in multiple states
  - Ex: sepsis, trauma

Udy AA et al. Clin Pharmacokinet 2010;49:1-16

Critically Ill Populations and PK Changes

Population	Physiological Changes	Pharmacokinetic Effects
Sepsis	Capillary leakage, augmented renal clearance, hypoalbuminemia	Increased Vd Increased Clearance
Burn	Capillary leakage, augmented renal clearance, hypoalbuminemia	Increased Vd Increased Clearance
Trauma	Augmented renal Clearance	Increased Clearance
MODS	Capillary leakage, hypoalbuminemia, hypoperfusion, end-organ failure	Increased Vd Decreased Clearance

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Roberts JA, Lipman J. Clin Pharmacokinet 2006;45:755-73
Udy AA et al. Clin Pharmacokinet 2010;49:1-16
Ulldemolins M et al. CHEST 2011;139:1210-20

Critically Ill Populations (Summary)

Issue	Possible solutions
Increased Vd	Loading doses
Augmented renal function	Use high doses Direct CrCl measurement
Decreased protein binding	TDM?
Organ failure	Adjust dose

Roberts JA, Lipman J. Clin Pharmacokinet 2006;45:755-73

How often do we get the dose wrong?

- DALI study: prospective, multi-center, pharmacokinetic, point-prevalence study
  - Mid-point and trough concentrations drawn and interpreted in relation to the MIC of the infecting organism

	Antibiotic (No. of Patients)					
Dosing and PK/PD Data	Cefazolin (n = 14)	Cefepime (n = 14)	Ceftriaxone (n = 33)	Doripenem (n = 13)	Piperacillin (n = 109)	Meropenem (n = 89)
Dosage per 24h, g	3.0 (3-4)	6.0 (5-6)	2.0 (2-4)	1.75 (1.5-3)	12.0 (12-16)	3.0 (3-4)
50% f_T>MIC achieved	100%	78.6%	97%	100%	80.6%	95%
100% f_T>MIC achieved	78.6%	78.6%	93.9%	76.9%	67%	69.7%

	Achieved 50% fT>MIC	Did not achieve
Overall population	84%	16%*
Prolonged infusion (33%)	93%	7%
Intermittent infusion (67%)	80%	20%

*Associated with clinical failure OR 0.68 (95% CI 0.52-0.91)

CHI Memorial / Roberts JA et al. Clin Infect Dis 2014;58:1072-83

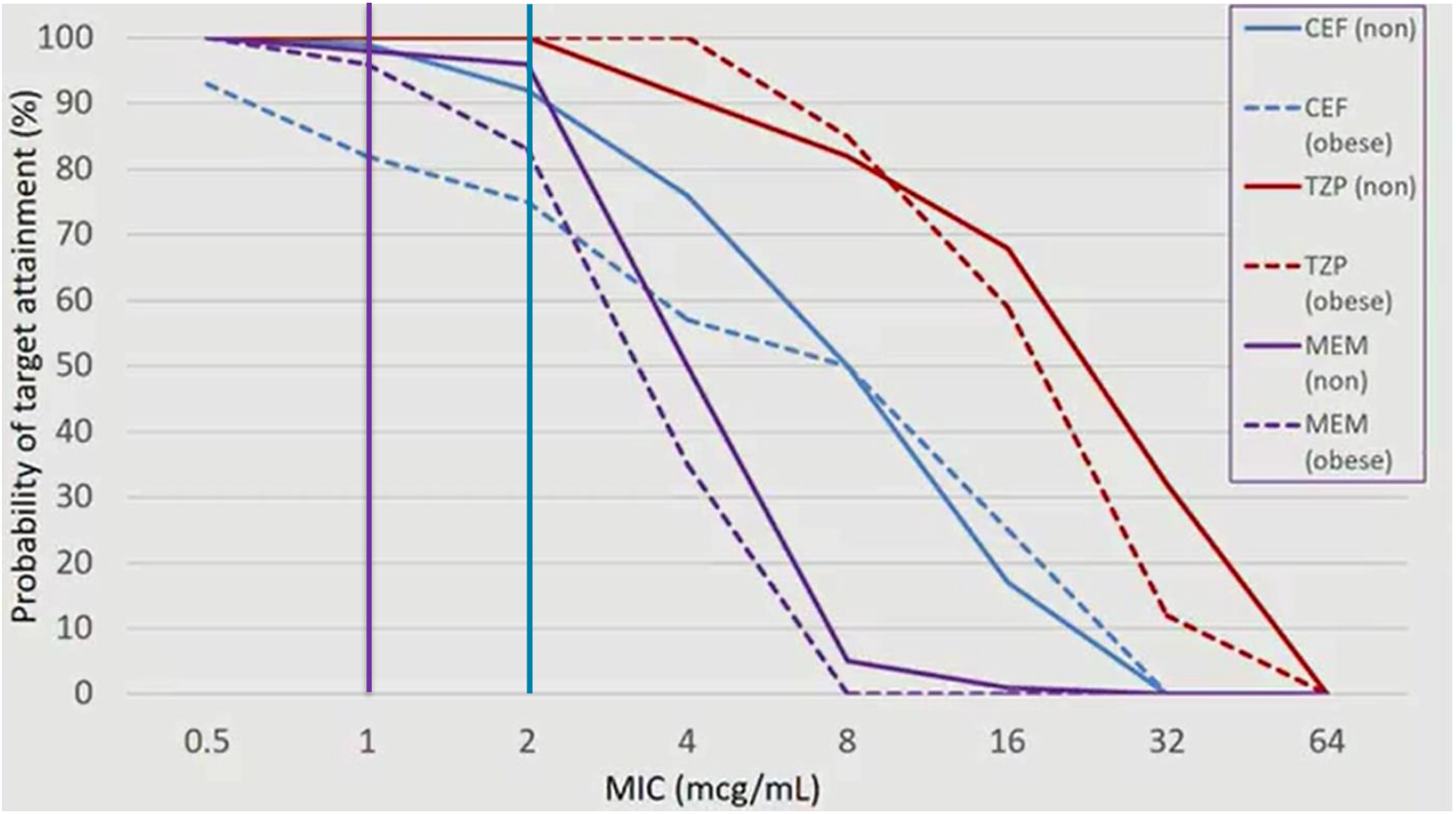
Obesity and Antibiotics

- Increased antibiotic failures compared to general population

- Obese population underrepresented in both PK and efficacy studies

- PK changes in obesity
  - Absorption – not significantly modified
  - Distribution
    - Max blood flow rate into fat <5% of cardiac output so hydrophilic drugs should not be greatly influenced
    - Volume of distribution increases
  - Metabolism – changes not well defined
  - Elimination – higher glomerular planar surface area (difficult to estimate)

PK Effects of Obesity in Infected Ill Patients



 / Roberts JA, et al. Int J Antimicrob Agents 2010;36:332-39.

Antibiotic dosing in obesity

- Meng et al., Pharmacotherapy 2017;37(11):1415-31

- 3 most commonly utilized beta-lactams
  - Piperacillin/tazobactam
    - 4.5g IV q8h (extended) – BMI≥30
  - Cefepime
    - Data is lacking but consider 2g q8h in critically ill + BMI ≥30
  - Meropenem
    - Obesity did not hinder achievement of PD targets
    - Consider on case by case basis

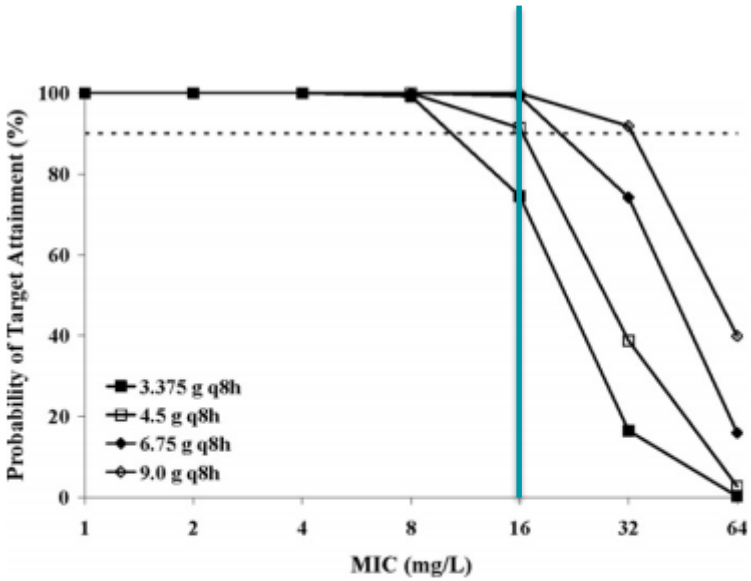
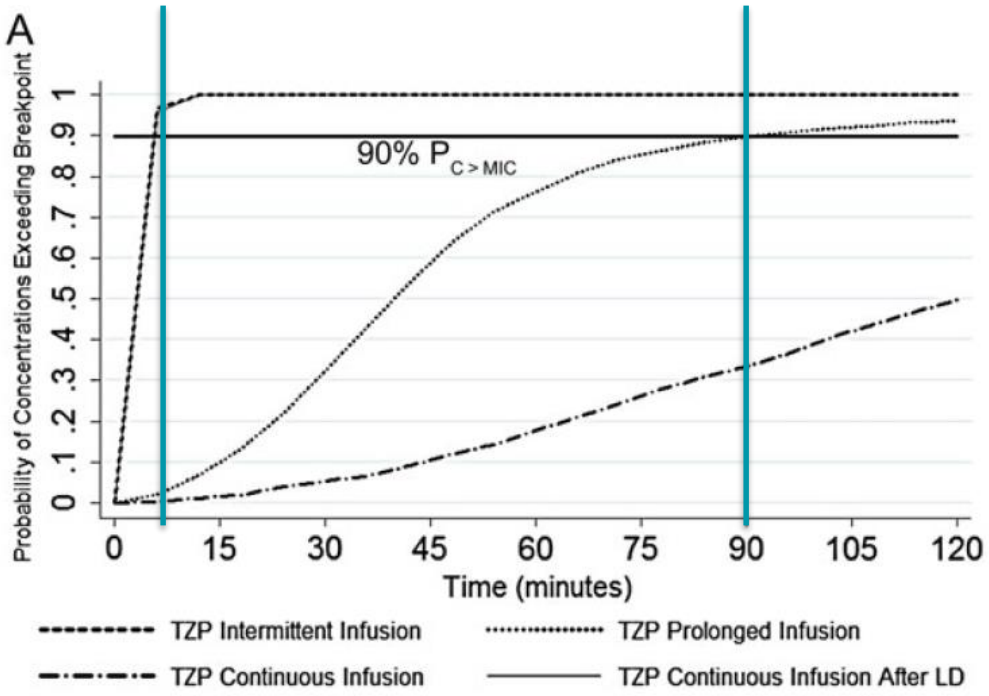


Fig. 2. Probability of target attainment at ≥50% *fT* > MIC for piperacillin/tazobactam, based on piperacillin serum concentrations, administered by prolonged infusion in obese patients. *fT* > MIC, time that unbound (or free) drug concentration remains above the minimum inhibitory concentration of a bacterial pathogen; q8h, every 8 h.

Zosyn loading dose rationale



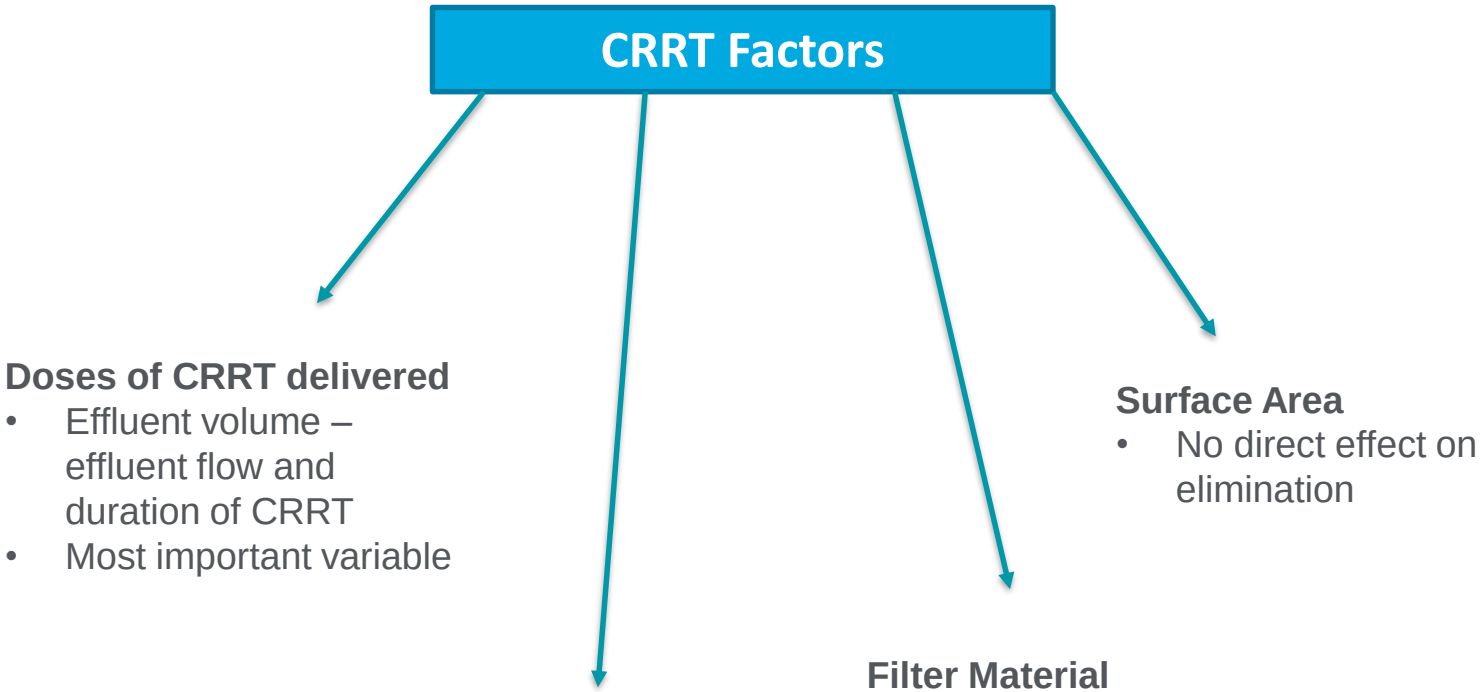
Piperacillin/Tazobactam (Zosyn®)	Loading Dose	BMI <30	BMI ≥30
CrCl > 20 ml/min or CRRT	4.5 gm IV x 1 dose (30min infusion), followed by BMI based dosing strategy	3.375 gm IV q 8 hrs (4 hour infusion)	4.5 gm IV q 8 hrs (4 hour infusion)
CrCl ≤ 20 or HD or peritoneal dialysis		3.375 gm IV q 12 hrs (4 hour infusion)	

Cefepime (Maxipime®)			
CrCl (ml/min)	**Febrile Neutropenia, Treatment of recent or confirmed infection with a GNR with an MIC of 8, critically ill with BMI ≥ 30**	**UTI, no sepsis**	**All other indications**
> 50	2 gm Q 8 hrs	1 gm Q 12 hrs	1 gm Q 6 hrs
30-49 or CRRT	2 gm Q 12 hrs	1 gm Q 24 hrs	1 gm Q 8 hrs
11-29	2 gm Q 24 hrs		1 gm Q 12 hrs
≤ 10 or HD	1 gm Q PM (give after dialysis)		

CRRT Modalities

Technique	Convection	Diffusion
Continuous venovenous hemofiltration (CVVH)	++++	-
Continuous venovenous hemodialysis (CVVHD)	+	++++
Continuous venovenous hemodiafiltration (CVVHDF)	+++	+++

CHI Memorial / Heintz BH, Pharmacotherapy 2009;29:562-577


CRRT Factors
Doses of CRRT delivered
• Effluent volume – effluent flow and duration of CRRT
• Most important variable
Blood Flow Rate
• Little effect on elimination
Filter Material
• Sieving coefficient can vary between filter materials for some antibacterials
Surface Area
• No direct effect on elimination

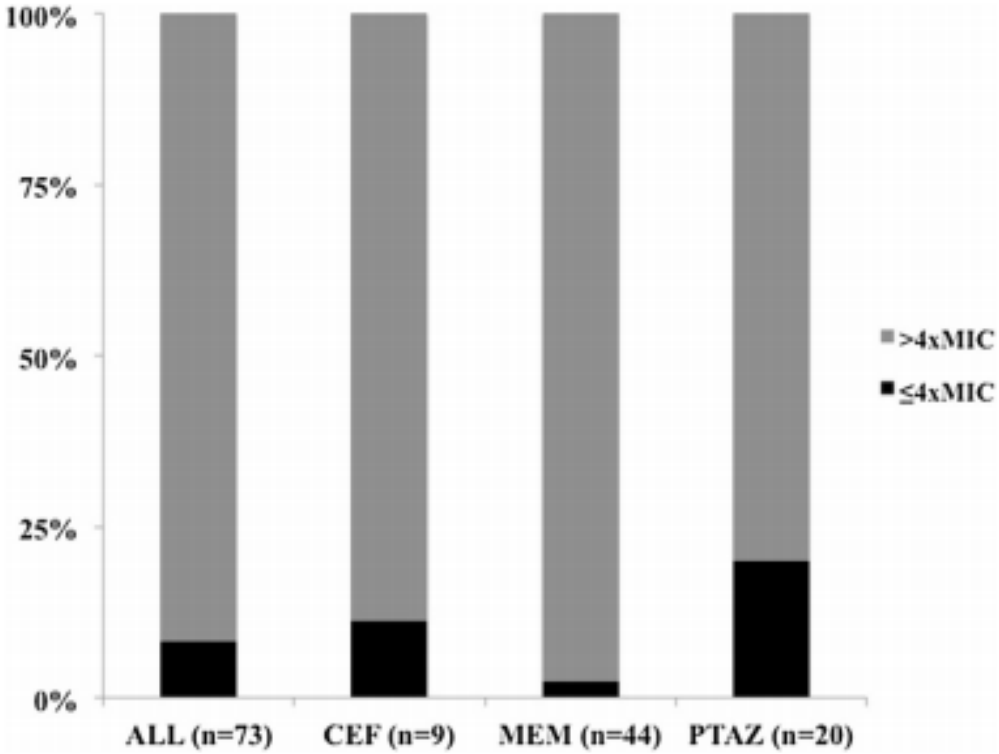
Drug Properties

- Increase in Vd
  - Larger loading dose needed
  - Decreased efficacy of CRRT removal

- Protein binding
  - Only unbound fraction of drug removed by CRRT

- In general, drugs with high Vds (>1L/kg) and high protein binding (>80%) are poorly eliminated by CRRT

Beta-lactam Concentrations in CRRT



- Doses of antibiotics based on renal function → proportion of inadequate serum concentrations ~10%
- Trade-off → 53% had very high levels, ? Toxicity concerns

CRRT Dosing Recommendations

- Assume ultrafiltration and dialysate flow rates of 1-2L/hr and minimal residual renal function
- Dosing recommendations in the literature particularly for CVVHD & CVVHDF are too low
- Consider loading doses

Heintz BH, Pharmacotherapy 2009;29:562-577
/ Lewis SJ, Semin Dial 2014;27:441-5

Drug	Loading Dose	Maintenance Dosage for CRRT			High Dose*
		CVVH	CVVHD	CVVHDF	
Ampicillin	2g	1-2g q8-12h	1-2g q8h	1-2g q6-8h	2g q4-6h
Ampicillin/sulbactam	3g	1.5-3g q8-12h	1.5-3g q8h	1.5-3g q6-8h	3g q6h
Aztreonam	2g	1-2g q12h	1g q8h or 2g q12h	1g q8h or 2g q12h	2g q8h
Cefazolin	2g	1-2g q12h	1g q8h or 2g q12h	1g q8h or 2g q12h	2g q8h
Cefepime	2g	1-2g q12h	1g q8h or 2g q12h	1g q8h or 2g q12h	1g q6h or 2g q8h
Ceftaroline	600mg	400-600mg q12h			600mg q8h
Ceftazidime/avibactam	2.5g	1.25g IVq8h			2.5g q8h (based on ceftazidime data)
Ceftolozane/tazobactam	3g	750mg q8h	1.5g q8h	1.5g q8h	1.5g q8h (data lacking for higher dose)
Ciprofloxacin	N/A	400mg q12-24h	400mg q12-24h	400mg q12h	400mg q8-12h
Levofloxacin	N/A	750mg q48h	750mg q48h	750mg q24h	750mg q24h
Meropenem	1g	500mg-1g q12h	500mg-1g q8-12h	500mg-1g q8-12h	500mg q6h/1g q8h
Meropenem/vaborbactam	4g	1-2g q8h (extended)			2g q8h (extended); based on meropenem data
Piperacillin/tazobactam	4.5g	3.375-4.5g IV q8h (extended)			

*Parameters:

- Ultrafiltration/dialysate flow rate of >2L/hr
- Residual renal function

Heintz BH, Pharmacotherapy 2009;29:562-57

Optimal Dosing in CRRT – A Moving Target

Changes in mode

Frequent filter changes or clogged filters

Alteration of flow rates

Off/On with access issues

Non-CRRT clearance