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Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

Monday, December 3, 2018
2:00 PM – 3:30 PM

Presenters:
Doug Fish, Pharm.D., BCCCP, BCPS-AQ ID
N. Jim Rhodes, Pharm.D., M.Sc., BCPS-AQ ID
Bruce A. Mueller, Pharm.D., FASN, FCCP, FNKF

Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Learning Objectives

- Identify critical factors that influence antibiotic exposure in patients with altered renal states.
- Evaluate alternative antibiotic dosing schemes to improve outcomes and facilitate care transitions.
- Select appropriate antibiotic regimens for patients with altered renal states.

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Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

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Objective

- Identify critical factors that influence antibiotic exposure in patients with altered renal states

Patient Case #1: K.G.

- K.G. is a 76 y.o. , 75 kg male who resides in a long-term care facility. He has a PMH significant for Type 2 DM, HTN, CAD, and stage 2 CKD. He has NKDA. He was hospitalized 2 weeks ago due to acutely altered mental status and chest pain.
- He now develops fever, increasing SOB, right-sided chest pain, and cough productive of purulent sputum. He is transported to the ED where the following are noted: BP 115/55 mm Hg, HR 121/min, RR 26/min, and Temp 38.9^{o}C; the patient is alert and oriented x 1. His BUN/SCr are 53/1.5 with UO = 20 mL/hr; chest X-ray is consistent with RLL pneumonia.
- He is given 2 L NS and started on cefepime + vancomycin

Based on K.G.'s history and clinical presentation, which of the following pharmacokinetic changes (compared to healthy individuals) would you expect to affect his antibiotics?

A Decreased clearance

B Increased volume of distribution

C Decreased protein binding

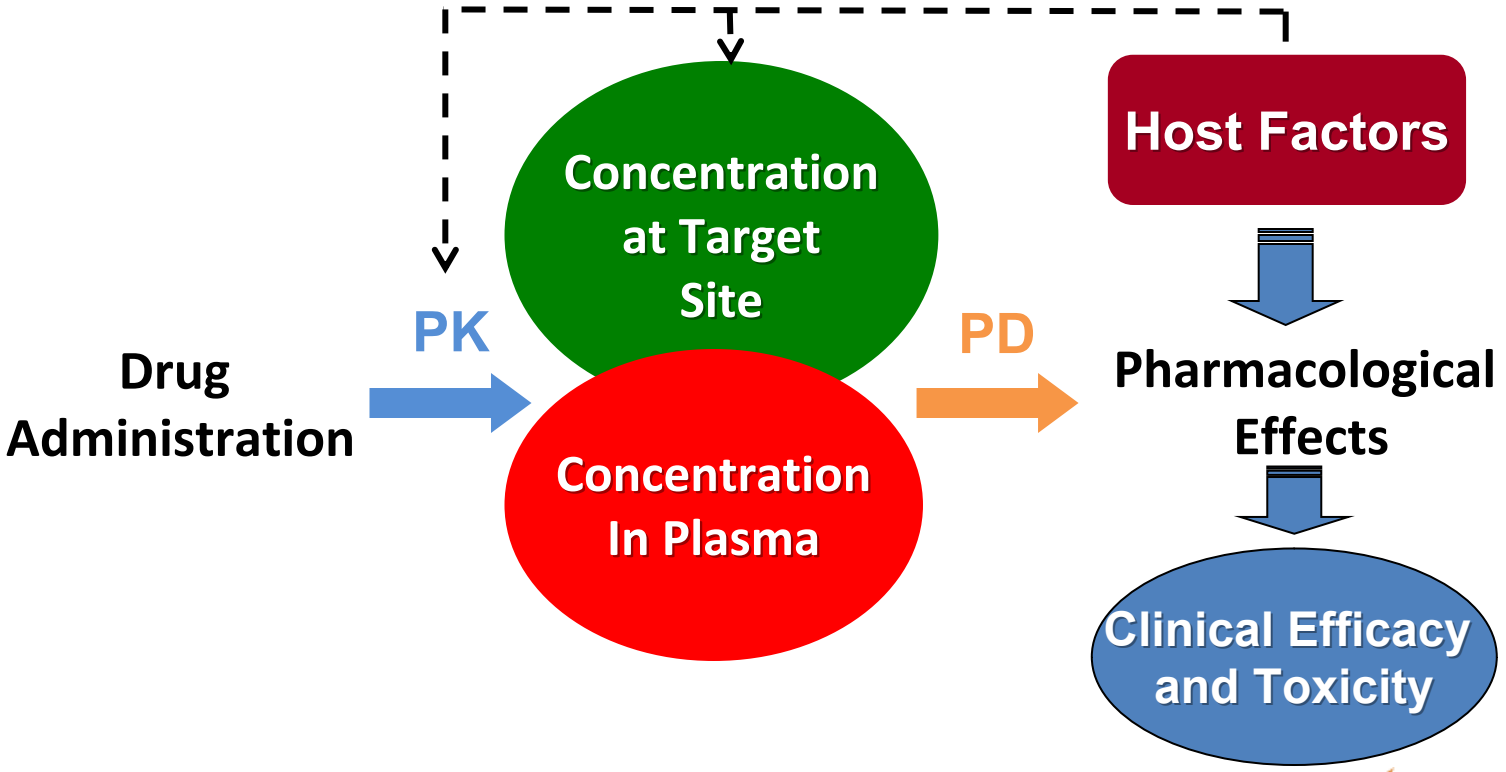
D All of the above

Renal Impairment in Hospitalized Patients

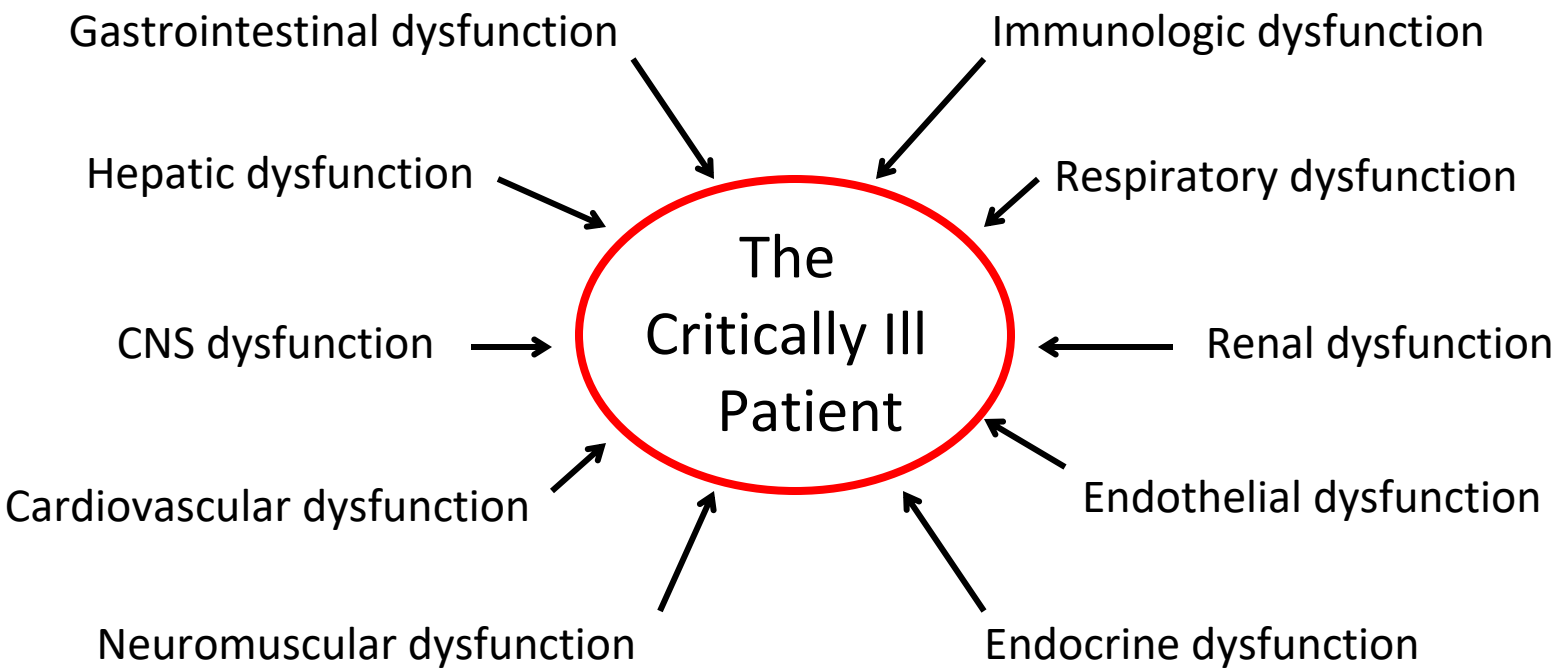
- Acute kidney injury (AKI) reported to occur in 4% - 23% of all hospitalized patients
  - Associated with infection in 10% - 30% of cases
- AKI occurs in up to 80% of patients with sepsis
  - Associated with increased mortality, hospital LOS, ICU LOS, cost
- One study found 31% of all infection-related hospitalizations occurred in patients with chronic kidney disease (CKD)
  - CKD also associated with increased hospital mortality, LOS, cost

Wang HE, et al. *Am J Nephrol* 2012;35:349-355.
Alobaidi R, et al. *Semin Nephrol* 2015;35:2-11.
Pannu N, et al. *JAMA* 2008;299:793-805.
Su G, et al. *Scientific Rep* 2017;7.

Relationship Between Pharmacokinetics and Pharmacodynamics



Alterations of Organ/Body Systems in Critically Ill Patients



Potential PK Alterations Related to Physiochemical Properties of Antibiotics

	Hydrophilic Drugs	Lipophilic Drugs
Volume of Distribution (Vd)	Small (0.1 – 0.8 L/kg)	Large (≥1 L/kg)
Area of Distribution	Primarily in extracellular fluids	Extensive intracellular penetration
Elimination (CL)	Predominantly renal	Predominant liver metabolism
Volume of distribution (Vd)	Vd ↑ or ↓ according to fluid shifts, fluctuations in body water	Not highly affected by fluid status
Changes in drug CL in critically ill patients	CL ↑ or ↓ according to changes in renal function	CL ↑ or ↓ according to changes in hepatic function

Adapted from Roberts JA, Lipman J: Crit Care Med 2009;37(3):840-851.

Physiochemical Classification of Antibiotics

- Hydrophilic antibiotics
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Aztreonam
  - Vancomycin
  - Linezolid
  - Polymyxins
  - Fluconazole
  - Aminoglycosides
  - Daptomycin
  - (Fluoroquinolones)
  - Acyclovir
- Lipophilic antibiotics
  - (Fluoroquinolones)
  - Macrolides
  - Tetracyclines
  - Rifampin
  - Clindamycin
  - Voriconazole
  - Posaconazole

PK/PD Alterations in Renal Impairment: More Than Just Decreased Renal Clearance

- Bioavailability
  - Alterations in absorption and/or time to Cmax for PO drugs
- Protein binding
  - Decreased due to albuminemia, ↓ binding affinity, competition for binding sites
- Volume of distribution
  - Often significantly increased due to fluid overload, ↓ protein or tissue binding
- Nonrenal clearance
  - Altered hepatic enzyme metabolism or transporter function
  - Nonrenal clearance may be ↑ in AKI and ↓ in chronic renal failure
- Pharmacodynamic alterations
  - Drug receptor site changes

PK Alterations: Volumes of Distribution (Vd)

- Attributed to numerous factors:
  - AKI and CKD
  - Aggressive volume resuscitation
  - Capillary leak syndromes
  - Hypoalbuminemia
  - Cachexia and muscle mass depletion
  - Ascites, peritoneal exudates, mediastinitis, large pleural effusions
  - Heart failure
  - Malnutrition
  - Acid-base disturbances
  - Burn injuries
- Alterations in Vd are not accurately predictable among individual patients
  - Individuals may also display significant changes in Vd over time

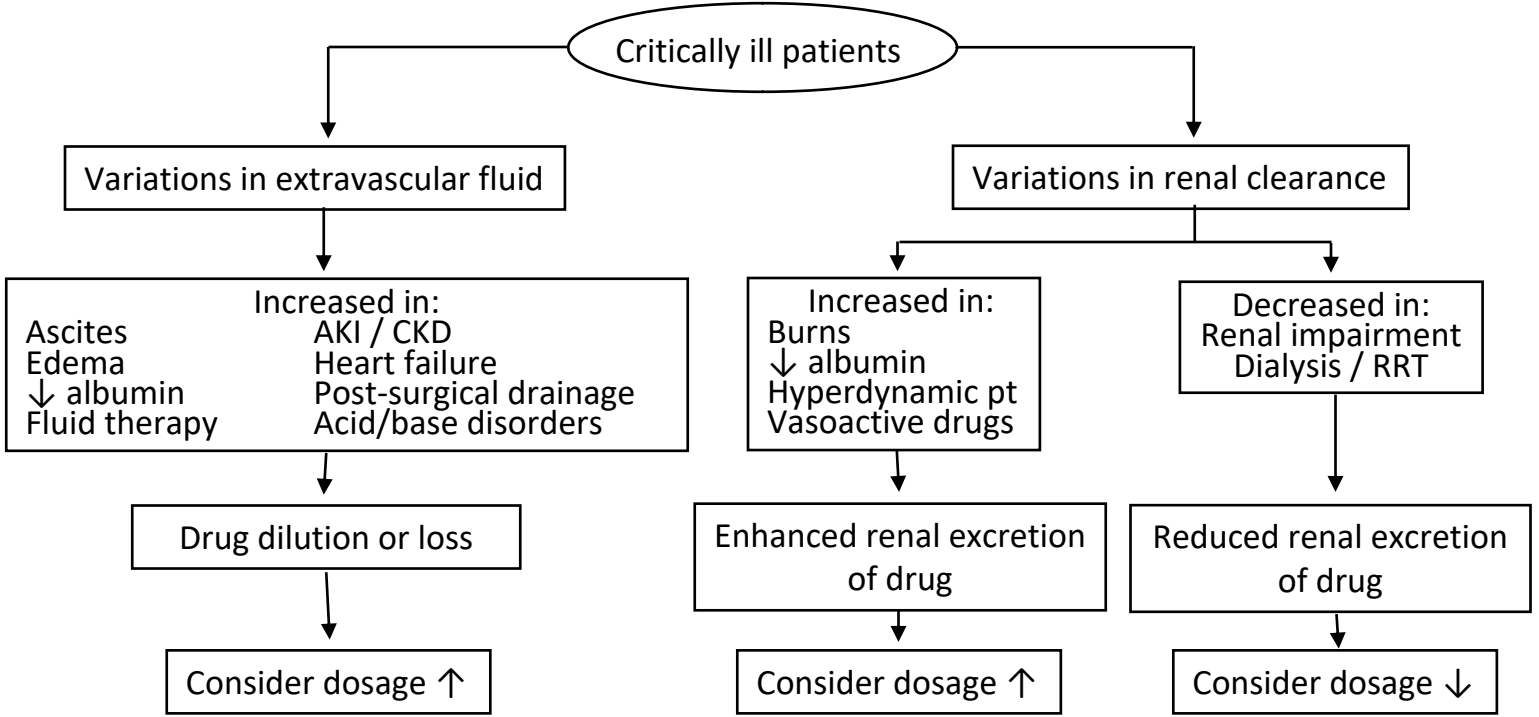
Fish DN. *Pharmacy Practice*. 2002;15(2):85-95.
Pea F, et al. *Clin Pharmacokinet* 2005;44:1009-1034.
Boucher BA, et al. *Crit Care Clin* 2006;22:255-271.

Pharmacokinetics of Cefepime in Patients with Various Degrees of Renal Function

Parameter	Creatinine clearance (mL/min)		
	Group 1: >100	Group 2: 60-100	Group 3: 11-59
$T_{1/2}$ (hr)	3.1 ± 2.6	7.6 ± 5.2	12.1 ± 6.3
CL (L/hr)	7.0 ± 4.3	4.4 ± 2.2	2.6 ± 1.1
V_{ss} (L/kg)	0.28 ± 0.25	0.46 ± 0.30	0.56 ± 0.30

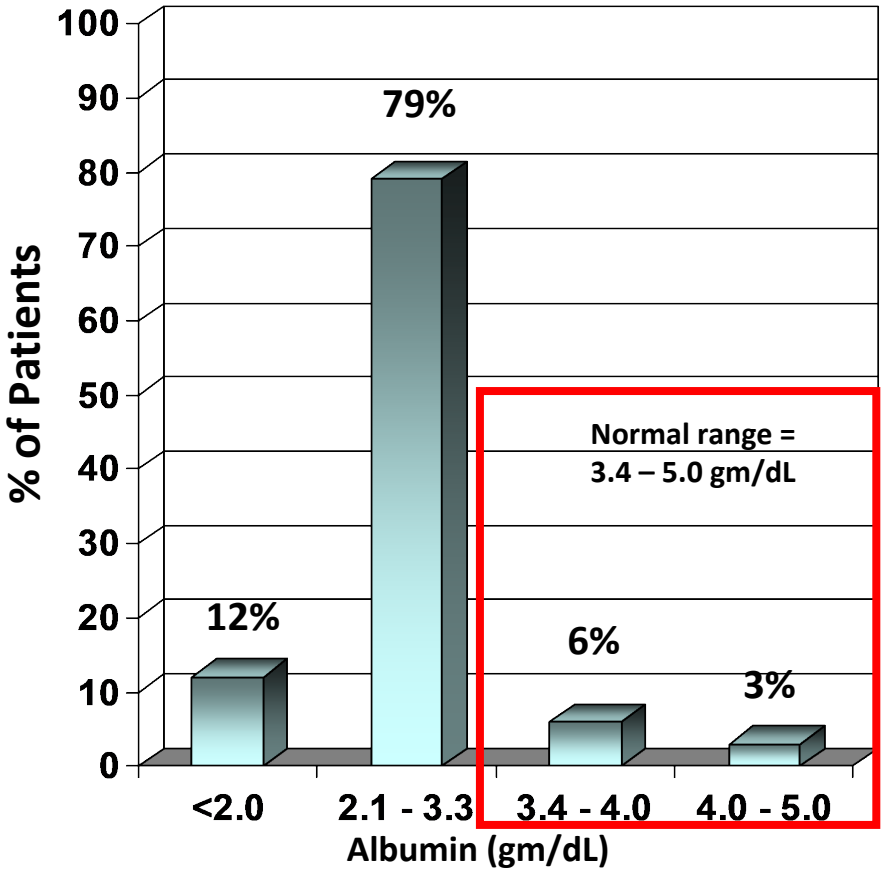
Tam VH et al. *Antimicrob Agents Chemother* 2003;47:1853-1861.

Factors Affecting Drug PK in ICU Patients and Clinical Recommendations



Adapted from Pea F, et al. *Clin Pharmacokinet* 2005;44:1009-1034.

Protein Binding Considerations in ICU Patients

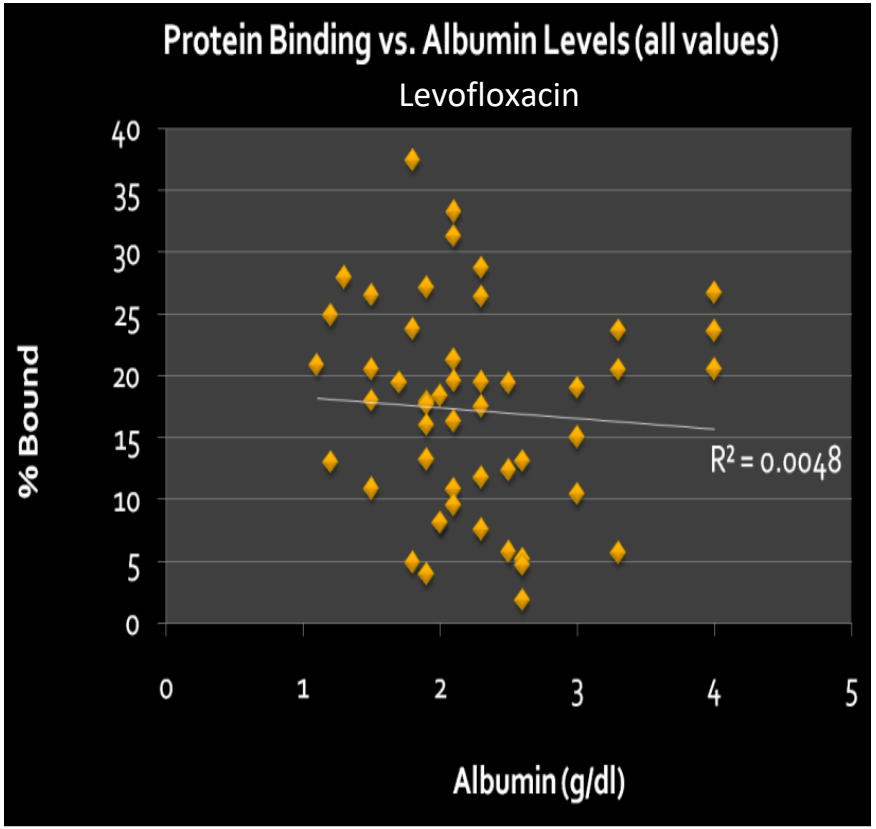


- Random sampling of 100 MICU patients at the University of Colorado Hospital found decreased albumin levels in 91%
  - Similar alterations found in SICU patients
- Total protein levels were also altered:
  - 47% of patients with decreased levels
  - Another 46% of patients had TP levels in lower half of normal range

Fish DN, unpublished data.

Altered Protein Binding of Drugs in the ICU

- Protein binding of levofloxacin determined in 20 MICU & Burn ICU patients at several time points
  - Binding in ICU (mean ± SD): 17.2 ± 8.4%
  - Normal binding: 24 - 38%
- Similar alterations reported for linezolid
  - Binding in sepsis/septic shock: 6.9 – 22.4%
  - Normal binding: 31%
- Pharmacodynamic relevance of these changes not clear



Hall AD, Fish DN, et al. 2009 ACCP Annual Meeting, Anaheim, CA; Alexander DP, DeRyke CA. 2009 SCCM Congress, Nashville, TN; Levaquin® Package Insert; Zyvox® Package Insert.

Case #1 Revisited:

Based on K.G.'s history and clinical presentation, which of the following pharmacokinetic changes (compared to healthy individuals) would you expect to affect his antibiotics?

A. Decreased clearance

B. Increased volume of distribution

C. Decreased protein binding

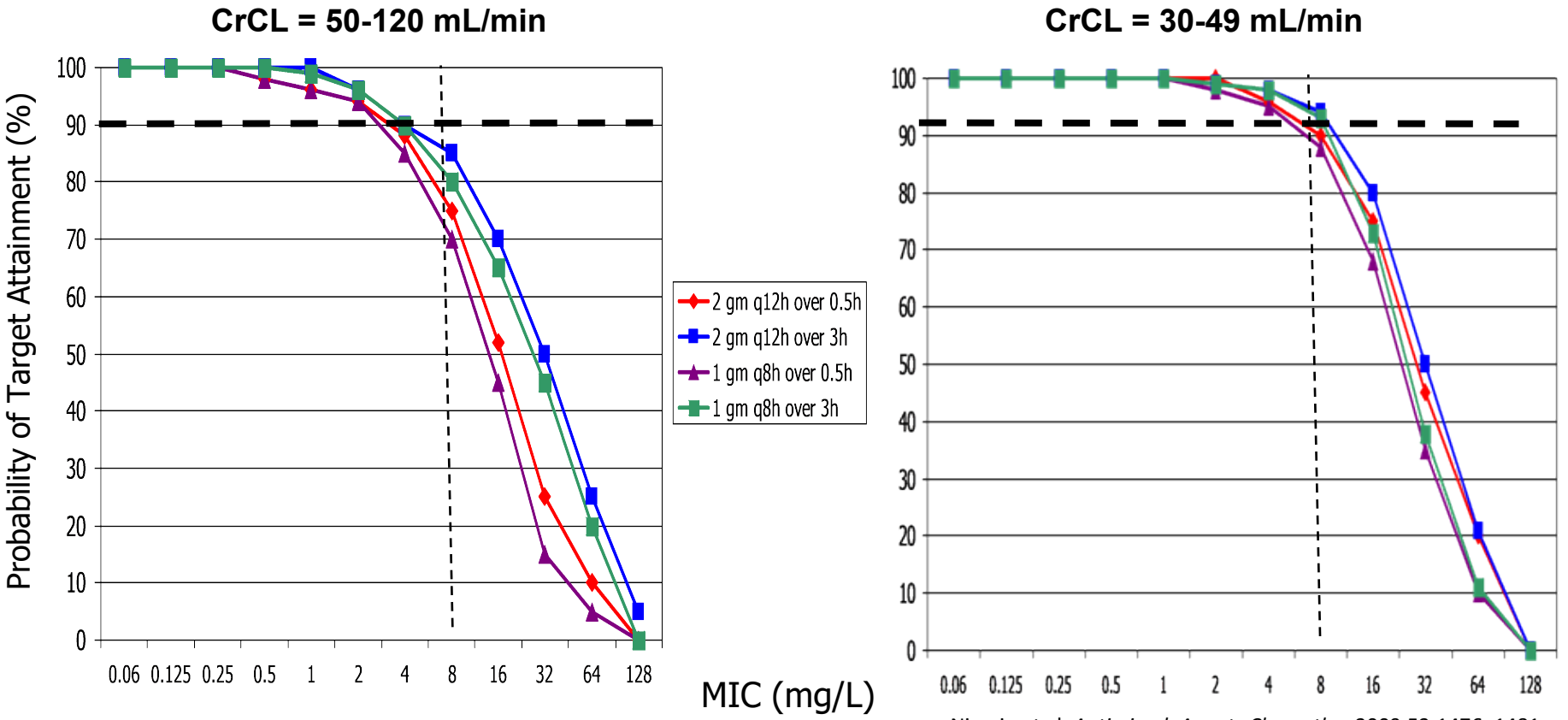
D. All of the above

What are Appropriate Pharmacodynamic Targets?

- Penicillins
  - *f*T > MIC of ≥50% of dosing interval
- Cephalosporins
  - *f*T > MIC of ≥60-70% of dosing interval
- Carbapenems
  - *f*T > MIC of ≥40% of dosing interval
- Fluoroquinolones
  - Gram-positive (*S. pneumoniae*): AUC/MIC >30
  - Gram-negative: AUC/MIC >125-250
- Aminoglycosides
  - Cmax/MIC >8-10
- Vancomycin
  - AUC/MIC >350-400

Craig WA. *Infect Dis Clin N Am* 2003. 17:479-501

Cefepime Pharmacodynamics in Patients with Varying Renal Function



Nicasio et al. *Antimicrob Agents Chemother* 2009;53:1476–1481.

Augmented Renal Clearance

- Generally defined as creatinine clearance >130 mL/min/1.73m^2
- Attributed to systemic inflammatory responses leading to ↑ cardiac output, ↑ renal perfusion
- Estimated to occur in 30%-65% of general ICU patients, up to 100% of patients with sepsis, trauma, CNS disorders such as TBI, SAH, infection
- Duration may be 1 week or more
- Difficult to accurately evaluate

Hobbs ALV et al. *Pharmacother* 2015;35:1063-1075.

Case #2

LF is to be treated with ertapenem for a severe intraabdominal infection. He is septic with AKI; his estimated creatinine clearance is 27 mL/min. The infection is known to be caused by a *Klebsiella*; susceptibilities are not yet known. Which of the following factors will likely have the most significant impact on achievement of desired antibiotic pharmacodynamic targets?

A. Alterations in Vd, CL

B. Pathogen MIC

C. Decreased protein binding

D. All of the above are equally important

Factors Affecting Drug Removal during Renal Replacement Therapy (RRT)

Elimination pathway	Renally eliminated drugs more readily removed
Volume of distribution (V_d)	> 0.7 L/kg: "large" V_d, not readily removed
Molecular weight	< 500 daltons: readily removed <1,500 daltons: potentially removed
Plasma protein-binding	> 80 to 90%: highly protein-bound, not readily removed
Dialysis membrane	Membrane material Membrane surface area Membrane permeability / pore size
Dialyzer system	Type of dialysis Flow rates of dialysate, blood, ultrafiltrate Pre- vs. post-filter replacement fluids Duration of dialysis Filter age

Comparison of RRT Modalities

Modality	Volume control	Solute removal
Intermittent HD	+++	++++
SLED	+++/++++	++++
CVVH	++++	+++/++++
CVVHD	++++	+++/++++
CVVHDF	++++	++++

- Drug clearance at any given dialysate/ultrafiltrate flow rates:
  - CVVHDF > CVVHD > CVVH > SLED ≥ IHD

HD = hemodialysis; CVVH = continuous veno-venous hemofiltration; CVVHD = continuous veno-venous hemofiltration; CVVHDF = continuous veno-venous hemofiltration; SLED = sustained low-efficiency dialysis.

General Principles of Drug Dosing during CRRT are Often Difficult to Apply

- CRRT is performed differently at almost every institution…
  - CVVH, CVVHD, CVVHDF, etc
  - IV replacement solutions given pre- or post-filter
  - Anticoagulation strategies
    - Citrate
    - Heparin
    - Nothing
  - Wide ranging effluent rates

Clinical Consequences of PK/PD Alterations on Drug Dosing

- Less predictable dose/response relationships
- Need for dosing changes, either higher or lower, to achieve desired responses
- Altered time to steady state & stable drug effects
- Potential for significant drug accumulation
- Increased potential for adverse effects/toxicities

Dosage Adjustment for Renal Impairment: Pharmacodynamic Considerations

- "Proper" adjustments may be clinically effective while reducing total drug exposure, drug cost & adverse effects

HOWEVER

- PK/PD of even high doses of many drugs already marginal
- Creatinine-based methods of assessing renal function notoriously inaccurate in many patients
- Trying to "fine tune" dose adjustments may place many patients at risk of treatment failure

THEREFORE

- Consider risks vs. benefits
- Don't be too hasty in making dosing adjustments

KEY TAKEAWAYS

1) **Significant PK alterations in patients with renal impairment may include changes in both CL and Vd**
   - Protein binding alterations are common but of unclear clinical relevance
2) **PK/PD alterations are difficult to accurately predict due to great variability in patient-specific parameters, RRT practices, etc.**
3) **Aggressive dosing of antimicrobials (at least during empiric therapy in high-risk patients) is often necessary optimize PK/PD performance**
   - Renal impairment may require higher daily doses of some drugs, not lower

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Session: Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

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Infectious Diseases Pharmacist
Northwestern Medicine, Chicago, IL

Emphasis of discussion

- Evaluate alternative antibiotic dosing schemes as they relate to
  - Improving clinical outcomes
  - Facilitating transitions in care

Case #2

- AJ is a 51 year old male presenting with fever, tachycardia, and night sweats.
  - HPI: Reports 4 day history of increasingly fatigue and night sweats after a recent road trip. Recalls leg was struck by piece of luggage with increasing tenderness.
  - PMH: significant for DM type 2 and hypertension
  - Allergies/AE: sulfamethoxazole-trimethoprim (rash), cefpodoxime (rash)
  - ROS: tachycardic and diaphoretic.
    - Skin: 2 x 4 cm LLE purulent rash. A/O x 3.
  - PE: Unwell appearing 5'6'' 150 kg male. Normal heart sounds no murmur noted.
    - Vitals: BP 100/75, RR 20, HR 118, Tmax 38.4°C, Sat. 95% on RA.
  - Initial lab results:
    - WBC: 13,000 cells/mm^3, PLT: 300,000 cells/mm^3, Tbili: 0.6 mg/dL, Scr: 0.5 mg/dL
  - ED course
    - Blood cultures are obtained
    - 2 L of normal saline and a one-time 2 gram dose of vancomycin
- AJ is admitted to the general medical service
  - Initial antibiotics: vancomycin 1.5 grams every 8 hr for sepsis d/t cellulitis

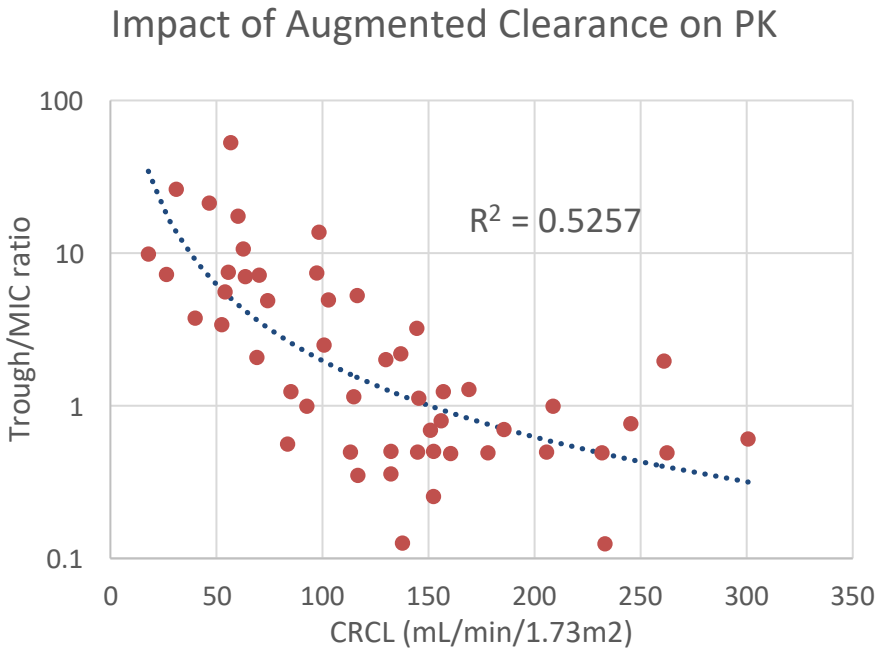
Case #2 Question 1

- Which of the following places AJ at an higher risk of augmented renal clearance?
  A. Receipt of a vancomycin loading dose
  B. Age ≥ 50 years
  C. Receipt of 2 L of intravenous fluids
  D. SOFA score ≤ 4

Udy AA, et al. *Chest*. 2012;142(1):30-39
Udy AA, et al. *Critical Care.* 2013; 17:R35

Altered renal states require altered dosing

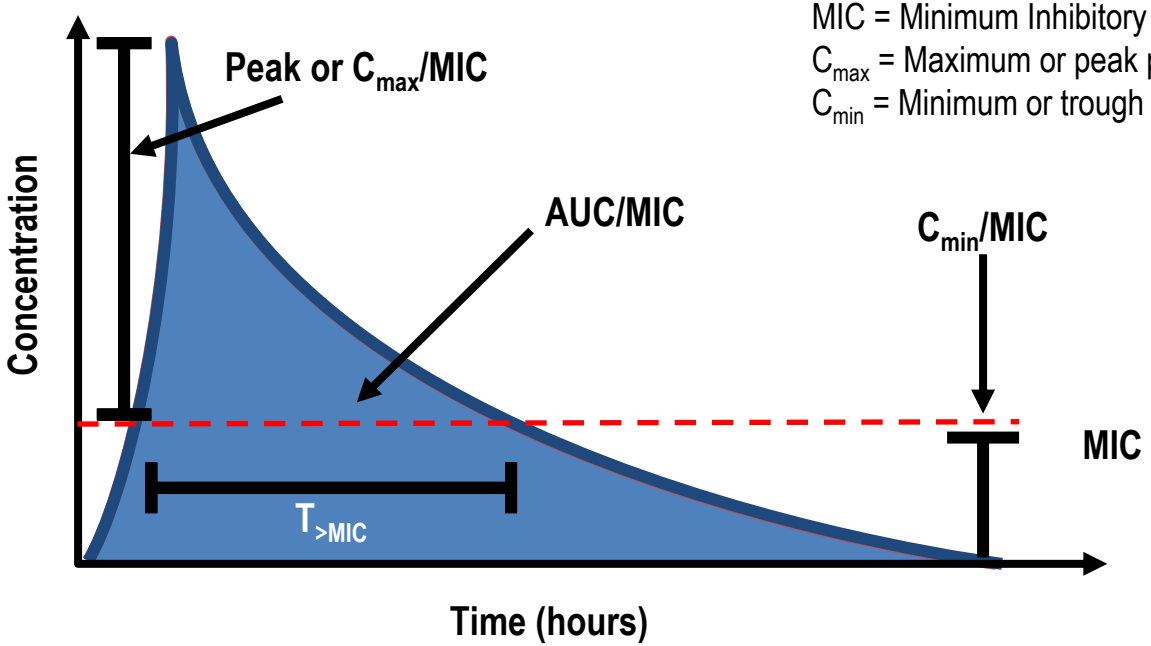
- Proposed mechanisms of augmented clearance
  - Elevated cardiac index
  - Receipt of vasopressors
- Various risk factors
  - Trauma, sepsis
  - Previously healthy
  - Younger (<50 years)
  - Febrile neutropenia



Udy AA, et al. *Clin Pharmacokinet*. 2010; 49: 1-16
Udy AA, et al. *Chest*. 2012;142(1):30-39
Udy AA, et al. *Critical Care*. 2013; 17:R35

PK/PD Measures

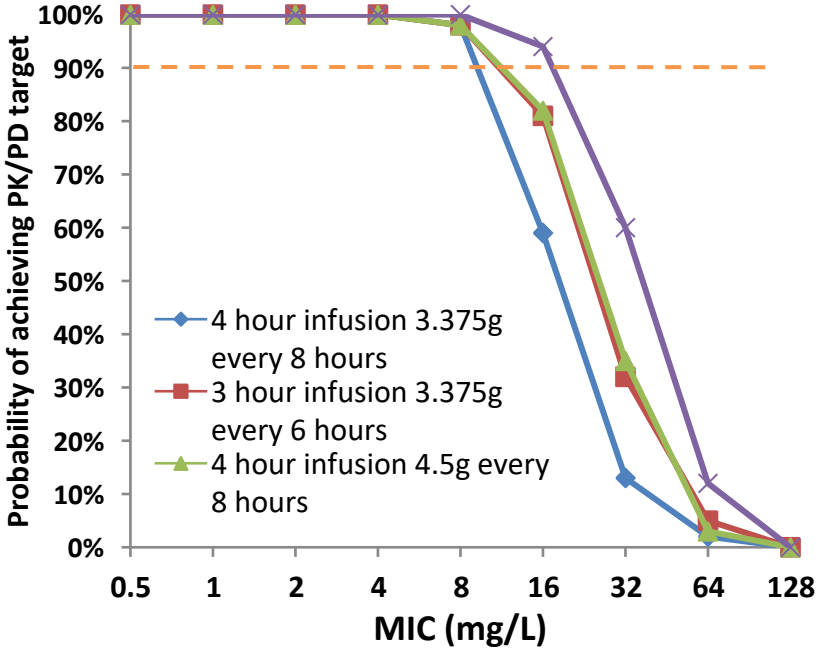
AUC = Area under the concentration–time curve
MIC = Minimum Inhibitory Concentration
C_{max} = Maximum or peak plasma concentration
C_{min} = Minimum or trough plasma concentration

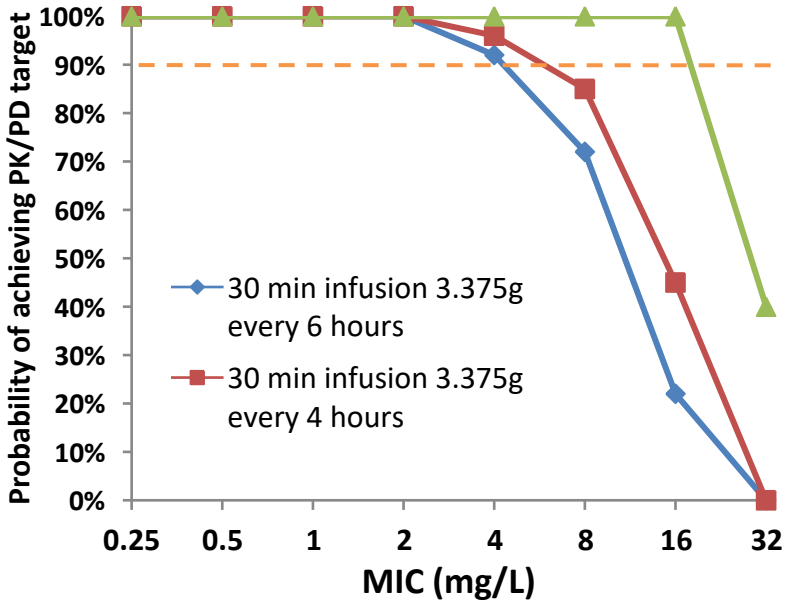


Scheetz MH, et al. *Am J Health Syst Pharm.* 2006;63:1346-60.

Critically ill patients: short on time

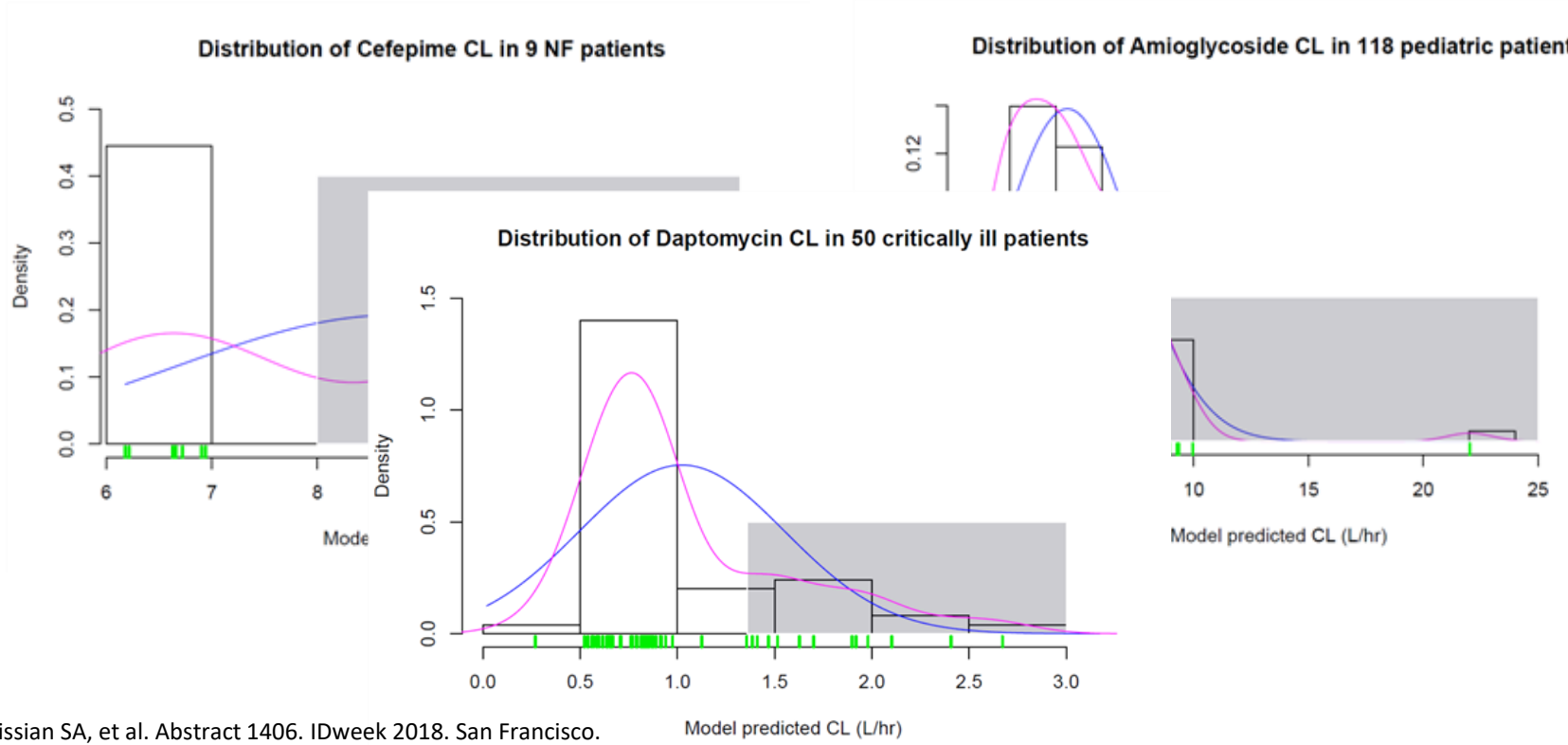
Probability of target attainment for piperacillin/tazobactam with goal $T_{>MIC}$ of 50%





Felton TW, et al. *Antimicrob Agents Chemother.* 2012;56:4087-94.
Lodise TP, et al. *Clin Infect Dis.* 2007;44:357-63.

Augmented clearance – decreased exposure



Avedissian SA, et al. Abstract 1406. IDweek 2018. San Francisco.
Rhodes NJ, et al. *Int J Antimicrob Agents*. 2017 Sep;50(3):482-486.
Falcone M, et al. *Clin Infect Dis*. 2013;57:1568-76.

Case # 2 Continued

- Six hours into his hospital admission, AJ becomes hypotensive with a blood pressure of 84/50 mmHg. His blood pressure has not responded to fluid resuscitation and the rapid response team is called to transfer him to the MICU.
  - A code sepsis alert is triggered and the pharmacist on call is tasked with initiating broad spectrum antibiotics.
  - The following dosing parameters are available:
    - TBW: 150 kg
    - IBW: 63.8 kg
    - ABW: 98.3 kg
    - Scr: 1.0 mg/dL

Case # 2 Question 2

- Which of the following best describes AJ's current renal function?
  A. 49 mL/min/1.73m^2 (Jelliffe & Jelliffe, TBW, BSA-Adjusted
  B. 71 mL/min/1.73m^2 (Chiou & Hsu, TBW, BSA-adjusted)
  C. 85 mL/min/1.73m^2 (Cockcroft Gault, ABW, BSA-adjusted)
  D. 129 mL/min/1.73m^2 (Cockcroft Gault, TBW, BSA-adjusted)
  E. AJ's renal function is unclear because urine creatinine is unavailable

Augmented renal clearance (ARC for short)

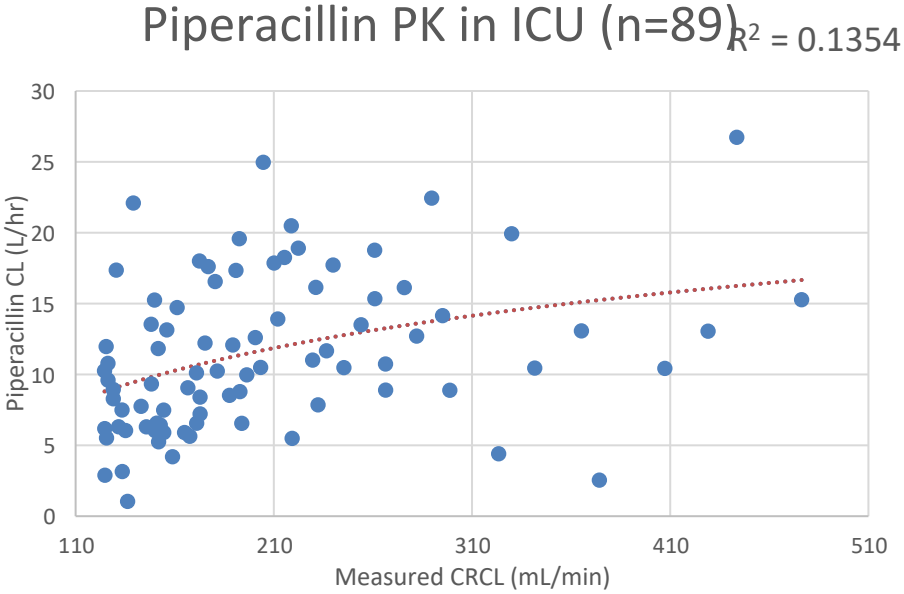
- Enhanced or supra-physiologic elimination of drug by kidneys
  - Quantifying renal clearance is difficult and time intensive
    - 8-hour urine collection
    - 24-hour urine collection
  - Defining “hyperfiltration” based on urinary creatinine
    - Glomerular hyperfiltration -> “Augmented Renal Clearance”
      - Consensus definition: > 130 mL/min/1.73m^2
      - Higher and lower cut points have also been proposed
  - Incidence varies 16-100% depending on population and definition
    - Etiology remains unclear
      - Increased cardiac output
      - Increased intravascular volume
      - Administration of vasoactive agents

Udy AA, et al. *Clin Pharmacokinet*. 2010;49:1-16.
Udy AA, et al. *Critical Care.* 2013; 17:R35

ARC you kidding me…

The relationship between CL and CRCL is complex…

For patients with high CRCL, linear adjustments to doses are unlikely to achieve PK/PD goals



Reasons for TDM:

- Increase efficacy
- Avoid toxicity
- Navigate PK complexities
- Monitor compliance

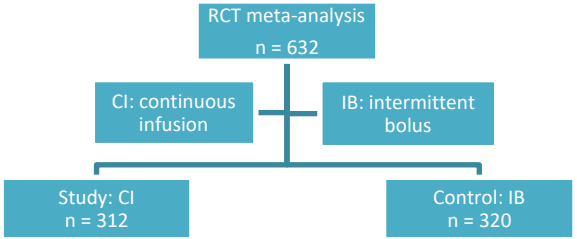
Jacobs A, et al. *Antimicrobial Agents and Chemotherapy* 2018; 62.

Augmented clearance and outcomes

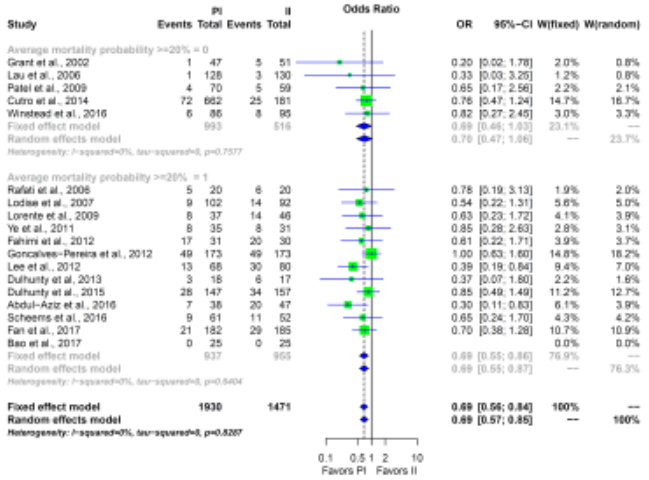
- BLING II ARC sub-study
  - CI or II beta-lactam
    - ARC define with 8 hr urine
    - CRCL >130 mL/min
  - Total eligible n=254
    - ARC present in 17.7%
  - Majority
    - On piperacillin (67%)
    - Pulmonary source (51%)
- Outcomes (ARC vs not)
  - ICU free days at D90
    - 21 vs 21 days (P=0.89)
  - Clinical cure at D14
    - 55 vs 73% (P=0.024 unadjusted)
  - Mortality at D90
    - 13.3 vs 19.6% (P=0.33)

Udy AA, et al. *Int J Antimicrob Agents*. 2017;49:624-630.

Continuous infusions (CI) to the rescue?



Roberts JA, et al. *Am J Respir Crit Care Med*. 2016;194:681-91.



Rhodes NJ, et al. *Crit Care Med*. 2018;46:236-243.

Meta-analyses of PI or CI beta-lactam

Roberts et al. [CI vs. IB]

- 30-day mortality
  - RR 0.73 (0.55-0.98)
- ICU mortality
  - RR 0.82 (0.58-1.16)
- Clinical cure
  - RR 1.32 (0.97-1.80)

Rhodes et al. [EI or CI vs. IB]

- All-cause mortality
  - OR 0.69 (0.56-0.84)
- Clinical cure
  - OR 1.77 (1.24-2.53)
- Microbiological cure
  - OR 1.22 (0.84-1.77)

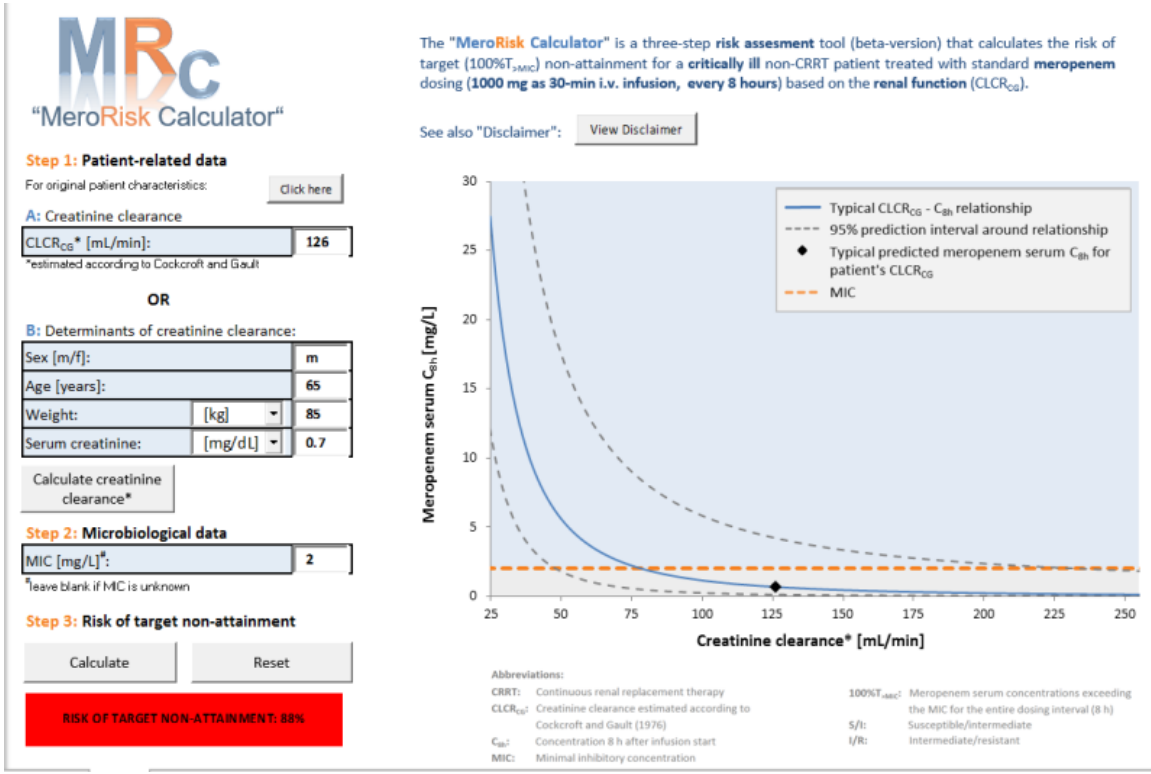
Augmented clearance: identify and mitigate

- Clinical risk assessment
  - ARC risk-factor score
    - Age ≤50 years
      - aOR 28.6 (95% CI 4.4-187.2)
    - Trauma
      - aOR 16.1 (95% CI 3.0-87.7)
    - Modified SOFA ≤4
      - aOR 5.1 (95% CI 1.0-25.0)
- Exposure assessment
  - Population PK approach
    - Modeling concentrations
    - Predicting exposures
    - Simulating regimens
  - Adaptive PK approach
    - Bayesian forecasting
    - Individualized dosing

Udy AA, et al. *Critical Care.* 2013; 17:R35

Predicting PK in critically ill patients

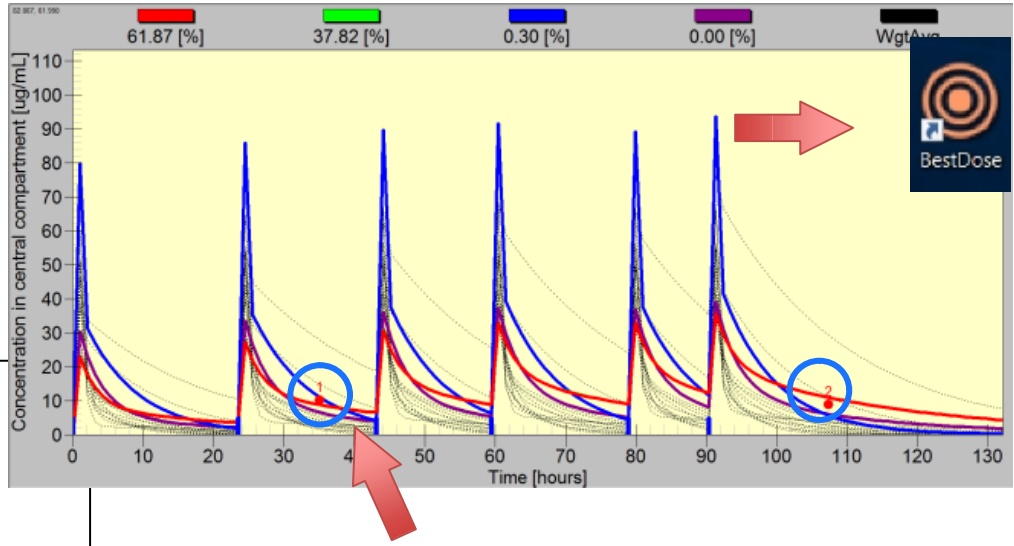
- Individualization
  - Population values
    - Easy fixed values
    - Lacks flexibility
  - Nomograms
    - Easy but static
    - Limited to original population of study



Ehmann L, et al. *Crit Care*. 2017;21:263.

Learning from the past to predict the future

Adaptive feedback:
Planning future regimen

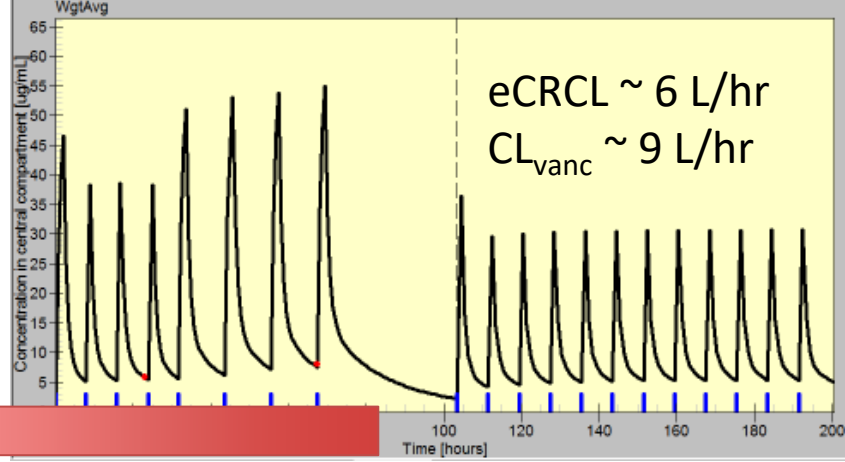


Planning Future Therapy			
Route	IV Option 6 - Control Central Compt. Conc. at Two Chosen Times after Dose		
Goal 1	36.00 [ug/mL]	Goal 2	12.00 [ug/mL]
Time 1	1.00 [hours]	Time 2	8.00 [hours]
ObjFunc	5.1098	AUC	3348.46

Dose #	Date	Time	Dose [mg]	AUC [ug/mL]	Total AUC [ug/mL]	AUC [mg/kg]	Total AUC [mg/kg]
1	08/13/13	13:16	368.5312	148.0518	2144.2286	64.6856	760.2807
2	08/13/13	21:16	546.2206	119.1068	2263.3354	46.2065	806.4872
3	08/14/13	05:16	593.5096	111.2772	2374.6126	40.9945	847.4816
4	08/14/13	13:16	606.7694	109.0718	2483.6844	39.5033	886.9850
5	08/14/13	21:16	610.5467	108.4388	2592.1232	39.0648	926.0498
6	08/15/13	05:16	611.6477	108.2513	2700.3745	38.9304	964.9802
7	08/15/13	13:16	611.9737	108.1924	2808.5668	38.8865	1003.8667
8	08/15/13	21:16	612.0532	108.1697	2916.7366	38.8701	1042.7368
9	08/16/13	05:16	612.0006	108.1512	3024.8878	38.8608	1081.5976
10	08/16/13	13:16	611.7141	108.1092	3132.9970	38.8463	1120.4439
11	08/16/13	21:16	610.6801	107.9718	3240.9688	38.8034	1159.2473
12	08/17/13	05:16	607.0061	107.4901	3348.4589	38.6554	1197.9027

Date	Time - Route	Dose [mg]	AUC [ug/mL]	Total AUC [ug/mL]	AUC [mg/kg]	Total AUC [mg/kg]
08/09/13	20:06 - IV	1000.0000	122.8323	122.8323	34.0926	34.0926
08/10/13	03:19 - IV	1000.0000	167.3207	290.1531	55.6231	89.7157
08/10/13	10:44 - IV	1000.0000	181.6216	471.7746	66.3727	156.0884
08/10/13	19:00 - IV	1000.0000	173.9378	645.7124	[illegible]	218.8384
08/11/13	03:00 - IV	1000.0000	171.9150	817.6274	[illegible]	279.8784
08/11/13	10:34 - IV	1000.0000	183.5234	1001.1508	[illegible]8633	346.7418
08/11/13	18:47 - IV	1000.0000	182.6756	1183.8264	66.4586	413.2004
08/12/13	03:10 - IV	1000.0000	172.1480	1355.9744	61.1560	474.3564
08/12/13	10:47 - IV	1000.0000	177.6817	1533.6561	63.9555	538.3119
08/12/13	18:32 - IV	1000.0000	188.2310	1721.8870	69.2846	607.5965
08/13/13	03:10 - IV	1000.0000	177.4659	1899.3529	63.8703	671.4668
08/13/13	11:19 - IV	1000.0000	96.8238	1996.1768	24.1283	695.5951

Making and revising plans based on patient-specific PK



Goal 1	32.00 [ug/mL]	Goal 2	12.00 [ug/mL]
Time 1	1.00 [hours]	Time 2	8.00 [hours]
ObjFunc	5.5773	AUC	2411.44

Dose #	Date	Time	Dose [mg]	AUC [ug/mL]	Total AUC [ug/mL]
1	05/21/14	18:30	1000.0000	86.1631	1463.3281
2	05/22/14	02:30	750.0000	80.2392	1543.5673
3	05/22/14	10:30	750.0000	82.8675	1626.4348
4	05/22/14	18:30	750.0000	84.5093	1710.9441
5	05/23/14	02:30	750.0000	85.5654	1796.5096
6	05/23/14	10:30	750.0000	86.2600	1882.7696
7	05/23/14	18:30	750.0000	86.7240	1969.4936
8	05/24/14	02:30	750.0000	87.0376	2056.5311
9	05/24/14	10:30	750.0000	87.2513	2143.7824
10	05/24/14	18:30	750.0000	87.3979	2231.1803
11	05/25/14	02:30		87.4990	2318.6794
12	05/25/14	10:30		92.7621	2411.4415

Dose #	Date	Time - Route	Dose [mg]	Central AUC [ug/mL]	Central Total AUC [ug/mL]	Peripheral AUC [mg/kg]	Peripheral Total AUC [mg/kg]
1	05/17/14	11:08 - IV	2000.0000	132.7400	132.7400	51.7671	51.7671
2	05/17/14	19:03 - IV	1000.0000	96.2269	228.9668	72.2643	124.0314
3	05/18/14	02:53 - IV	1000.0000	100.6503	329.6171	82.1052	206.1366
4	05/18/14	11:09 - IV	1000.0000	95.8612	425.4784	78.7252	284.8618
5	05/18/14	18:44 - IV	2000.0000	194.6722	620.1505	156.5160	441.3779
6	05/19/14	06:48 - IV	2000.0000	208.1597	828.3102	168.3039	609.6817
7	05/19/14	18:35 - IV	2000.0000	216.8165	1045.1267	182.4621	792.1438
8	05/20/14	06:33 - IV	2000.0000	332.0383	1377.1650	372.0627	1164.2066

AUC_{24} revised ~ 250

If MIC ≤ 0.5, still meeting "goal" but perhaps safer

AUC_{24} initial ~ 550

Case #2 Continued

- AJ is treated with empiric vancomycin 1.5 g IV every 8 hours and piperacillin-tazobactam 3.375 g IV every 6 hours over 4 hr for sepsis and cellulitis.
  - Hospital day 1: blood culture Gram stain reveals Gram-positive Cocci.
  - Hospital day 2: Surgical drainage and debridement of pyomyositis performed
  - Hospital day 3: blood cultures speciate as *Staphylococcus aureus* (MSSA)
  - Hospital day 4: Surgical cultures speciate MSSA and *E. coli*.
    - Relevant susceptibilities and MICs for the *E. coli* are as follows:

–	R	≥32	mcg/mL	Ampicillin
–	R	≥32	mcg/mL	Ampicillin/Sulbactam
–	R	≥8	mcg/mL	Cefazolin
–	S	≤1	mcg/mL	Ceftriaxone
–	S	4	mcg/mL	Cefepime
–	R	>4	mcg/mL	Ciprofloxacin
–	S	≤0.25	mcg/mL	Meropenem
–	S	8	mcg/mL	Piperacillin-tazobactam
–	R	>4/76	mcg/mL	Trimethoprim/sulfamethoxazole

Case #2 Question 3

- It is currently hospital day 5 and AJ is clinically improved and stabilized on the general medicine floor. Which of the following regimens would be the most appropriate for an outpatient transition for AJ?
  A. Ertapenem 1 gram every 24 hr IVP
  B. Cefepime 3 g / 24 hr via elastometric pump
  C. Ceftriaxone 2 g every 24 hr IVP
  D. Piperacillin-tazobactam 12 g / 24hr via elastometric pump

Making plans that work in-house and at home

- Elastomeric pumps
  - 10 mL/hr over 24hr
    - Piperacillin 12 g/day
    - Cefazolin 6 g/day
    - Cefepime 3 g/day
    - Flucloxacillin 8 g/day
- Stability at 0, 12, and 24 h
  - Mean change in concentration
    - -2%
    - +4%
    - -4%
    - -11%

<u>Mean (SD) temperatures during pump use:</u>

Kept at waist at night	30.9°C (0.9°C)
Kept at head of bed	26.2°C (1.0°C)
Outdoor excursions	26.2°C (3.3°C)

Voumard R et al. J Antimicrob Chemother. 2017;72:1462-1465

KEY TAKEAWAYS

1) **KEY TAKEAWAY**
Augmented renal clearance is of increasing interest and intense focus among critically ill population due to reduced PK/PD target attainment.

2) **KEY TAKEAWAY**
Pharmacists have at their disposal the means and expertise to identify and mitigate augmented clearance using individualized assessments.

3) **KEY TAKEAWAY**
Patients receiving extended or continuous infusions are at increased risk for medication errors during care transitions. Judicious use of outpatient infusions may be necessary to optimize PK/PD for serious infections.

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Session: Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

Bruce A. Mueller, Pharm.D., FCCP, FASN, FNKF
Professor & Associate Dean of Academic Affairs
University of Michigan College of Pharmacy
Ann Arbor, Michigan

Objective

- Select appropriate antibiotic regimens for patients with altered renal states

Patient Case 1

49 KG male is admitted to the ICU with an AKI secondary to sepsis. Patient is oliguric with SCr 4.3mg/dL. Due to the AKI, the patient is started on CRRT at 2L/hr effluent rate.

If Cefepime started, how should it be dosed?

Pkg Insert – no CRRT recommendations, but 1g LD followed by 500 mg Q24 is HD recommendation.

Aronoff et al. Green Book - 1-2 g q12h

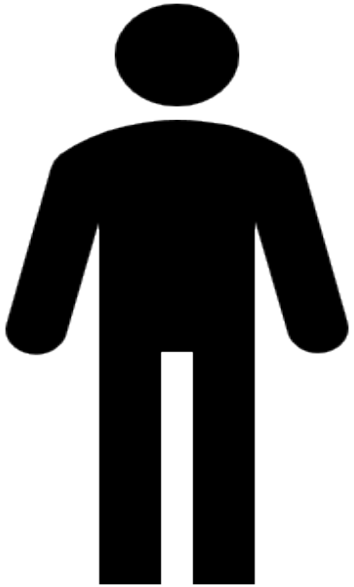
Trotman et al. CID 2005 - 2 g q12h

What cefepime dose do you choose?

A. 1gm LD followed by 500 Q 24
B. 1 Gm Q 12h
C. 2 Gm Q 12h
D. More?

Patient Case 2

129 KG male is admitted to the ICU with an AKI secondary to sepsis. Patient is oliguric with SCr 4.3mg/dL. Due to the AKI, the patient is started on CRRT at 2L/hr effluent rate.



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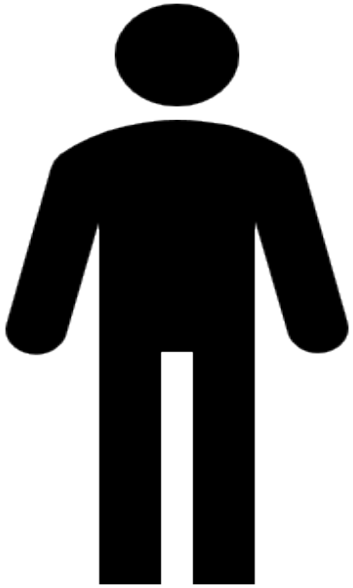


Dosing in critically ill patients with AKI…

"There are known knowns. These are things we know that we know.

There are known unknowns. That is to say, there are things that we know we don't know.

But there are also unknown unknowns. There are things we don't know we don't know."

Donald Rumsfeld

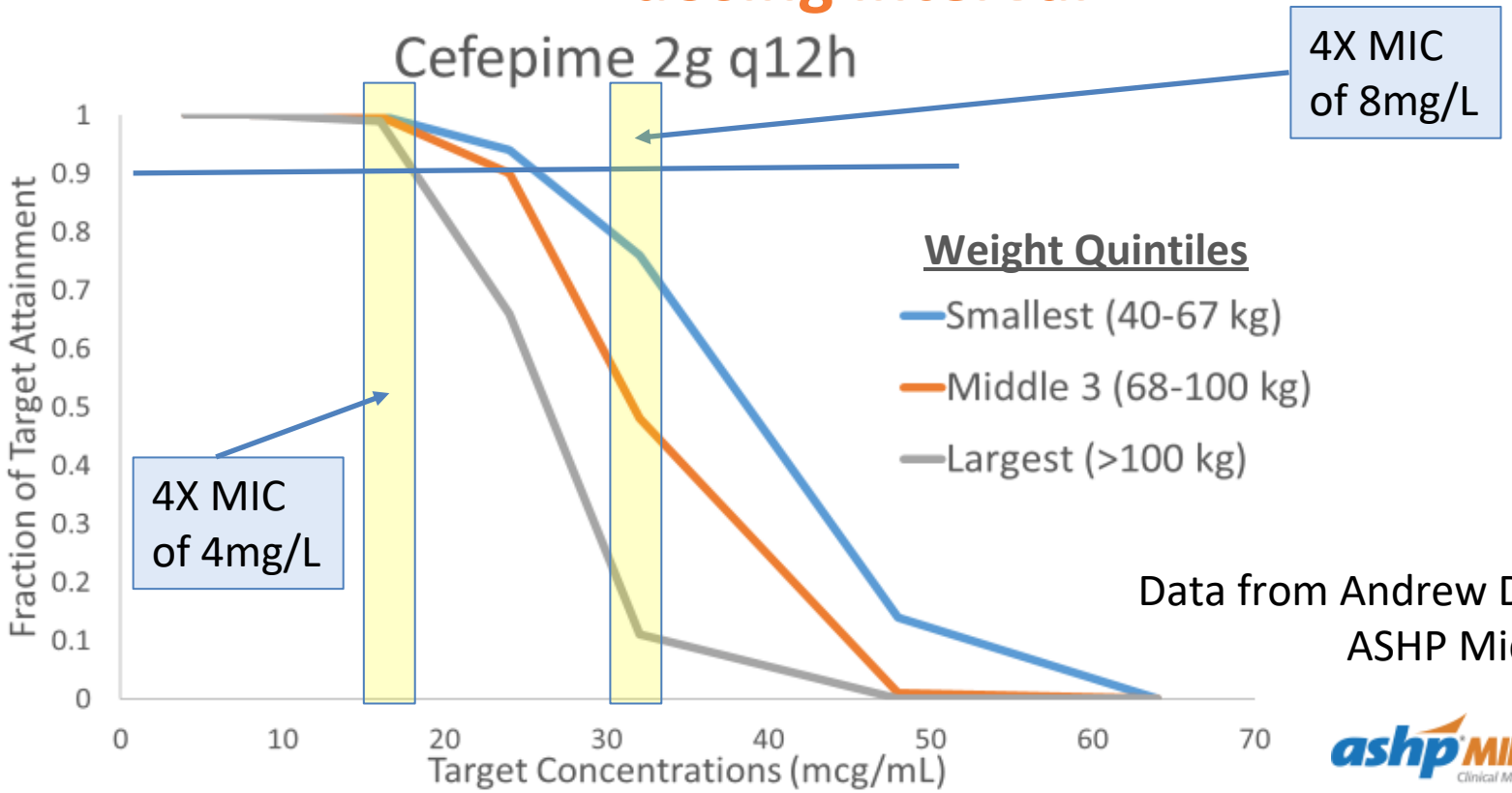
When dosing in RRT we have few metrics to base drug dosing on…

Known Knowns	Known Unknowns
Demographics (age, weight, sex, race)	Serum concentrations at site of action
RRT Operating Characteristics (rates, frequency, HD filters)	Volume of Distribution
Serum Creatinine	Non-Renal Clearance
Urine Output	Actual GFR

Monte Carlo Simulations for Cases 1 & 2

- Build virtual patients with pharmacokinetic parameters gleaned from published studies in patient population
  - Critically ill patients receiving CRRT (4 cefepime trials)
  - Of size (84.1 ± 19.6 kg) seen in CRRT patients (ATN Trial)
  - Receiving contemporary CRRT rates (25 mL/kg/h) (ATN Trial)
- Choose pharmacodynamic targets associated with good outcomes (e.g. >60% time free drug concentration >MIC)
- Dose 5000 virtual patients with each dosing regimen and see how many meet pharmacodynamic targets. (>90% is goal)
  - Shaw AR, Mueller BA. Adv Chronic Kidney Dis. 2017;24:219-227
  - U Michigan P4s, **Kristina Kan** & **Andrew Dodson** presenting their results at student posters at this ASHP meeting.

MCS of Cefepime & Patient Size: PD Target = 4X MIC of either 4 or 8 mg/L for 60% of dosing interval



N=5000

Data from Andrew Dodson 2018 ASHP Midyear Poster

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Monte Carlo Sim Results: PTA for daptomycin 8mg/kg Q24h by body weight: 24-48h

AUC 24-48h at MIC 1 mg/L *N= 5000 subjects*			
	AUC/MIC≥ 666	AUC/MIC<666	Total
Smallest 1000 pts body weight	873	127	1000
Largest 1000 pts body weight	969	31	1000
Total	1842	158	2000
Chi Square p< 0.0001			

Data from Kristina Kan, UMich P4 Student
2018 ASHP Midyear Poster

Smallest 1000 body weight (kg): 60 ± 5.6 (46 - 68)
Largest 1000 body weight (kg): 114 ± 13 (101 - 177)

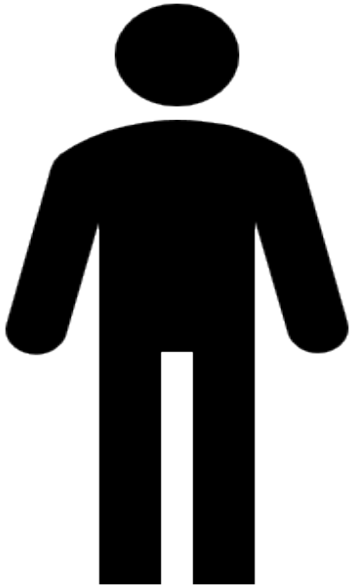
When dosing in RRT we have few metrics to base drug dosing on…

Known Knowns	Known Unknowns
Demographics (age, weight, sex, race)	Serum concentrations at site of action
RRT Operating Characteristics (rates, frequency, HD filters)	Volume of Distribution
Serum Creatinine	Non-Renal Clearance
Urine Output	Actual GFR

Can I break the renal dosing rules?

- Patient size (Known Known) in our cases should be “permission” for you to break rules.
  - Therapeutic Index

- When else can/should I break the rules?
  - Adjusting doses for renal function at admission
  - Adjusting doses for renal function in ICU AKI

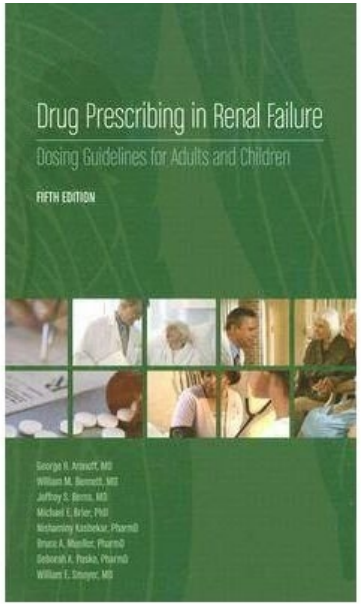


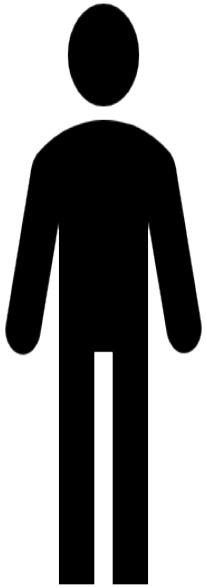
Patient Case 3

85 kg, 61 yo AA male is admitted to the hospital with apparent pneumonia. Patient's admission SCr 2.0mg/dL. Broad spectrum antibiotics to be started as we wait for culture results.

Upon which of the following should renal dose adjustments should be made?

MDRD "e-GFR":	39 mL/min
CKD-EPI:	40 mL/min
Cockcroft Gault:	47 mL/min
Modified CG for wt	41 mL/min



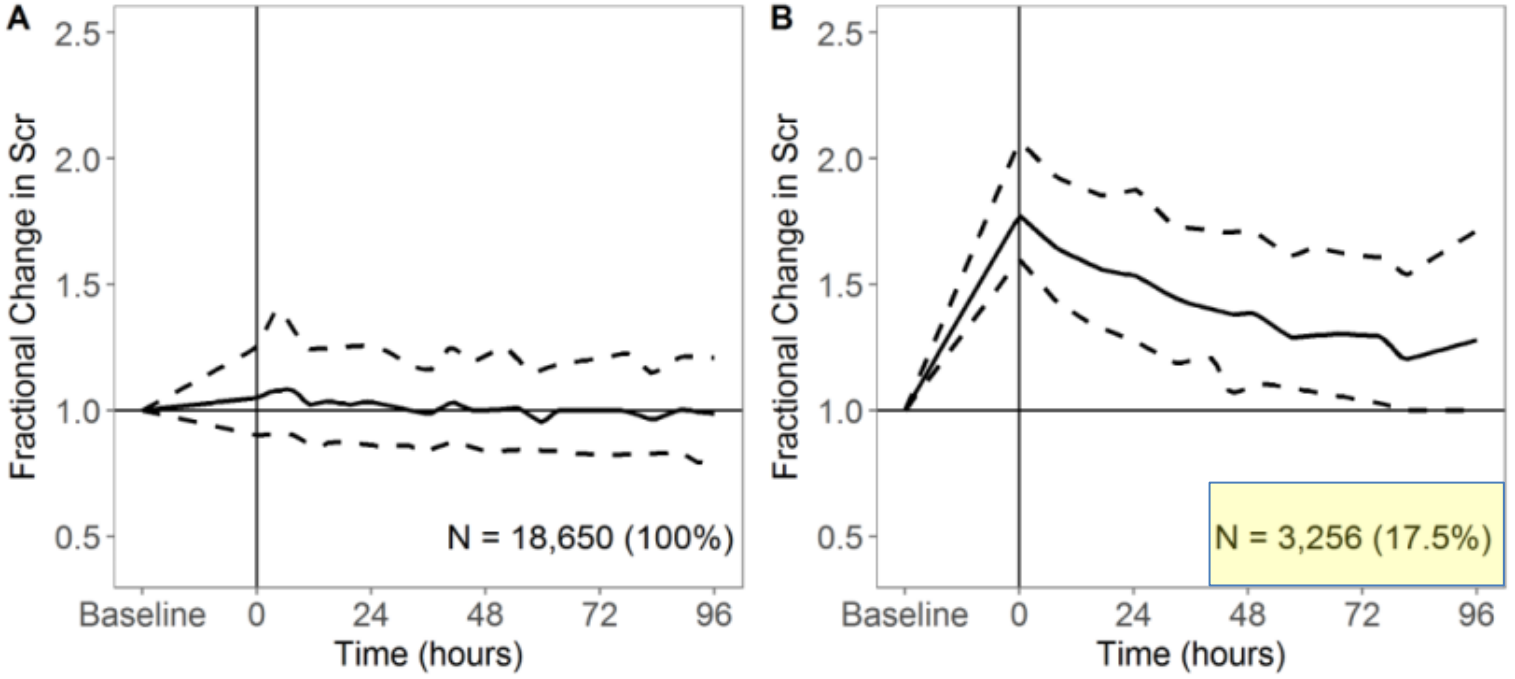


Pharmacists should ALWAYS adjust antibiotics for renal impairment, right?

- Patients admitted to Michigan Medicine with infectious diagnoses between January 2006 and April 2018 (n= 18,650)
  - Pneumonia
  - Complicated urinary tract infection
  - Complicated intra-abdominal infection
  - Acute bacterial skin/skin structure infection
- 3256 (17.5%) had AKI with an absolute increase in SCr of 0.3 mg/dL
- 57.2% of those diagnosed with AKI met no KDIGO criteria for AKI at 48 hours

RL Crass, KA Rodvold, BA Mueller, MP Pai; Renal Dosing of Antibiotics: Are We Jumping the Gun? Clinical Infectious Diseases 2018 (in press)

Serum Creatinine for First 48 hrs of Admission

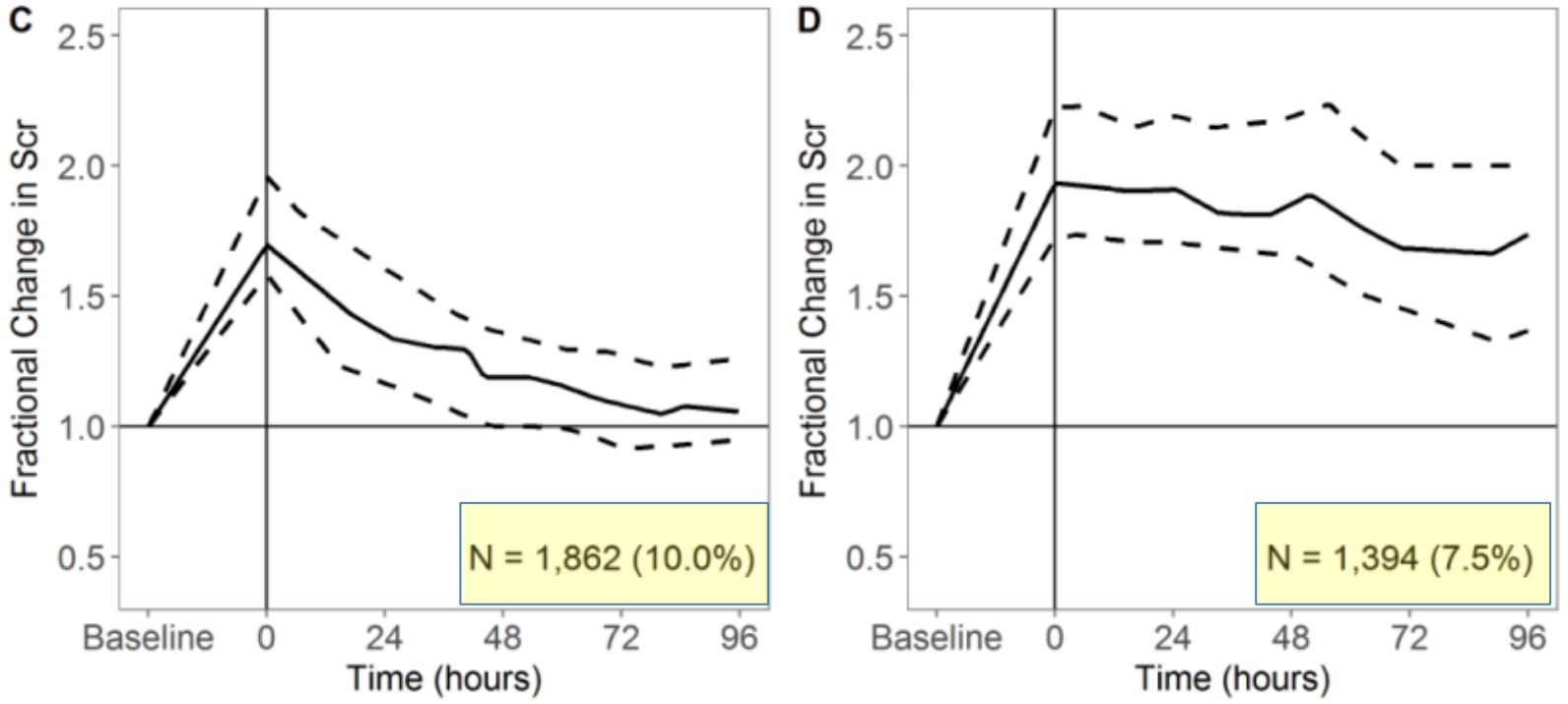


All admissions

Patients with AKI at admission

Adapted from RL Crass, KA Rodvold, BA Mueller, MP Pai. Clin Infect Dis 2018

Serum Creatinine for First 48 hrs of Admission



Adapted from RL Crass, KA Rodvold, BA Mueller, MP Pai. Clin Infect Dis 2018

Patient Case 3 revisited…

85 kg, 61 yo AA male is admitted to the hospital with apparent pneumonia. Patient's admission SCr 2.0mg/dL. Broad spectrum antibiotics to be started as we wait for culture results.

Upon which of the following should renal dose adjustments should be made?

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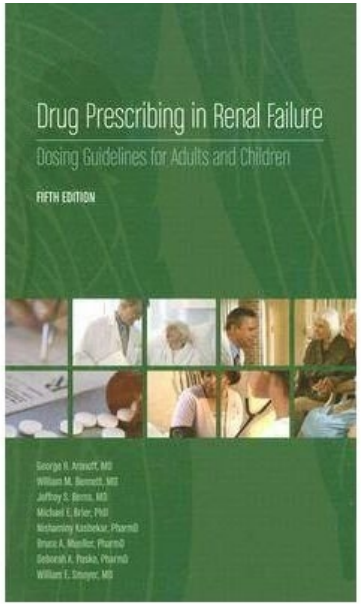
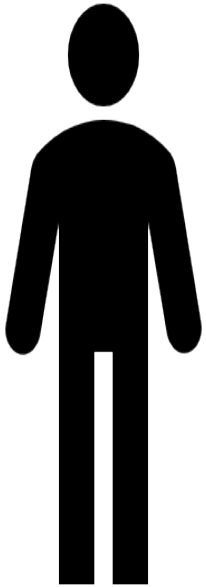


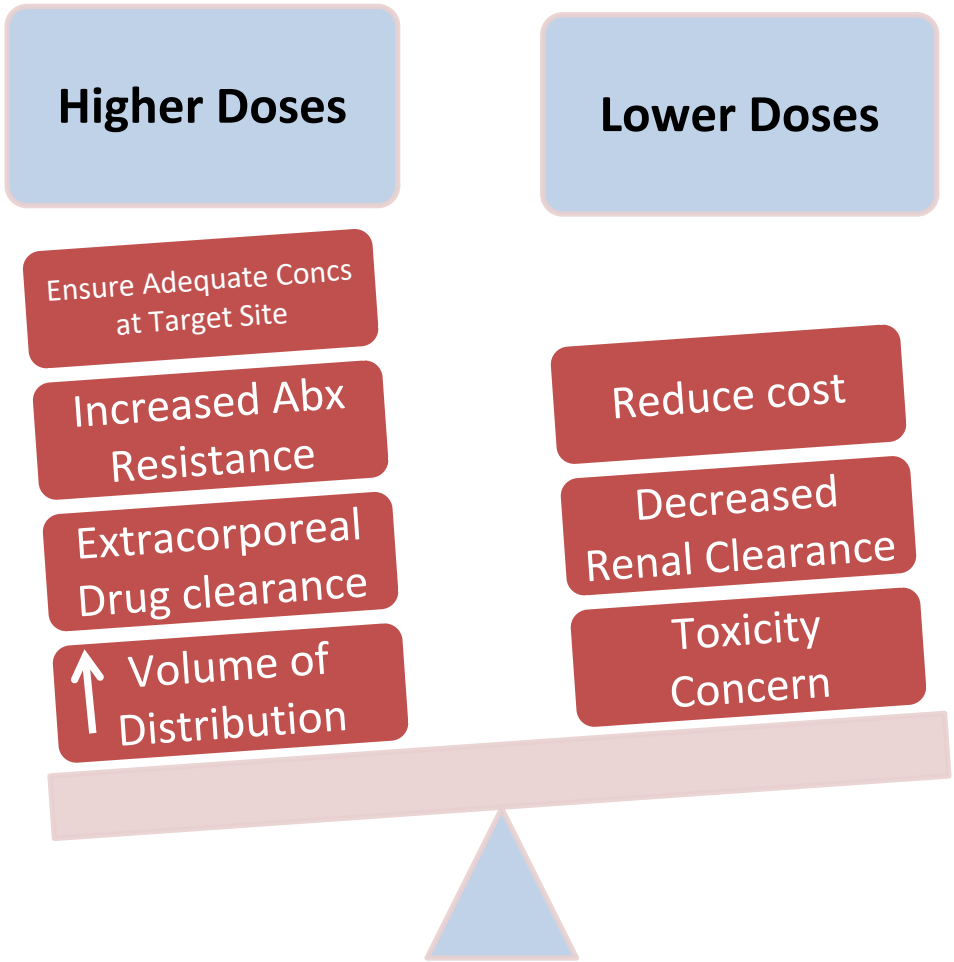


The mortality rate of CRRT patients is 30-50%, and the #1 cause of death is infection...

Of last 10 CRRT patients at your institution…
How many experienced symptoms of too high antibiotic concentrations?

A. 0-1 patient
B. 2-3 patients
C. 3-4 patients
D. 4 or more patients

Difficult Balance in Antibiotic Dosing Clinicians' Dilemma



Adapted from Lewis SJ, Mueller BA. *J Intensive Care Med.* 2014

Do We Meet Pharmacodynamic Targets in CRRT?

- 53 CRRT patients receiving meropenem, pip-tazo, cefepime or ceftazidime had serum assayed.
- Serum concentrations remained >4X MIC of Pseudomonas spp. for the recommended time
  - 81% patients treated with Meropenem 1000mg Q 12h
  - 71% with Piperacillin/Tazobactam 4.0/0.5 g Q 6h
  - 53% with Ceftazidime 2000 mg Q 12h
  - 0% with Cefepime 2000 mg Q 12h

- Seyler L et al: Recommended b-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care 2011;15:R137

Pharmacokinetic Changes in AKI

PK Change	Ability to Reach Pharmacodynamic Target
Fluid Overload	Reduced Ability
↓ Serum Albumin / ↓ Protein Binding	Mixed Effects
Retained Non-renal Clearance	Reduced Ability
Aggressive CRRT	Reduced Ability
Augmented Renal Clearance	Reduced Ability

How should a clinician decide on antibiotic dosing in ICU RRT patients??

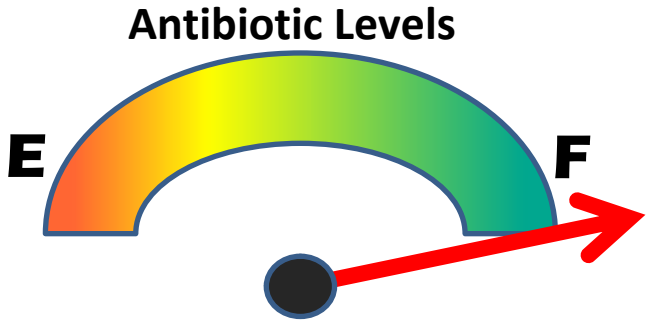
- **Therapeutic Index for most antibiotics is pretty wide (PCNs, Ceph, Carbapenems, etc)**
- **Will AKI at admission persist?**
  - **(Known Unknown)**
- **Should I give everyone a “normal renal” dose for their entire admission to be sure they are “therapeutic?**

What if I give “normal” antibiotic doses in CRRT patients?

- Beumier M, et al. β-lactam antibiotic concentrations during continuous renal replacement therapy. Crit Care. 2014; 18(3): R105.1

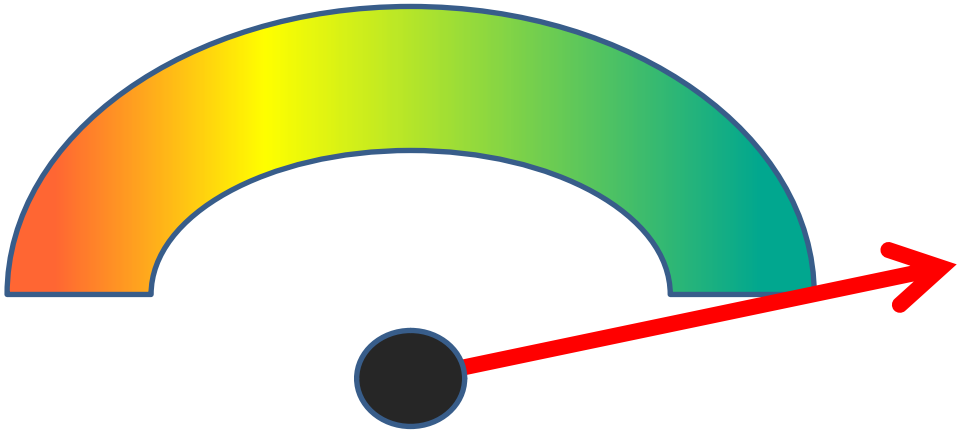
- 50 consecutive CRRT patients got Full Dose Antibiotics
  - Ceftaz/Cefepime 2g Q8 - Pip-Tazo 4 g Q6 - Meropenem 1 g Q8

- 90% patients met or exceeded pharmacodynamic goals
- 53% had dangerously high antibiotic levels



Can we improve ICU survival in patients with AKI?

Antibiotic Levels



KEY TAKEAWAYS

1) **PHARMACOKINETIC CHANGES IN AKI MIGHT BE A REASON TO BREAK RENAL DOSING RULES**
   Example: Fluid overload might mean larger doses, esp loading doses.

2) **CONSIDERING RRT IS IMPORTANT, CONSIDERING PATIENT IS MORE IMPORTANT**
   Example: A large patient often needs larger doses, in spite of pkg insert. Consider whole patient, not just RRT

3) **SOMETIMES BREAKING RENAL DOSING RULES IS OKAY**
   1. AKI often transient. Dosing as normal renal function for first day or two unlikely to cause toxicity and ensures adequate concentrations
   2. Augmented Renal Clearance

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Session: Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

Monday, December 3, 2018
2:00 PM – 3:30 PM

Presenters:
Doug Fish, Pharm.D., BCCCP, BCPS-AQ ID
N. Jim Rhodes, Pharm.D., M.Sc., BCPS-AQ ID
Bruce A. Mueller, Pharm.D., FASN, FCCP, FNKF