MAYO CLINIC

Better Cef than Sorry:
Beta-Lactam Monitoring in the ICU

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Learning Objectives

- Describe pharmacokinetic alterations of critical illness and the implications for beta-lactam optimization
- Recognize the potential role of beta-lactam therapeutic monitoring in predicting drug effectiveness
- Identify the potential role of beta-lactam therapeutic monitoring in recognizing drug toxicity

Pre-Question

An 82-year-old woman with a past medical history of heart failure, COPD, recurrent UTIs, and ductal carcinoma *in situ* is admitted to the MICU with fevers and hypotension.

What factors do you consider when assessing patients for potential pharmacokinetic changes?

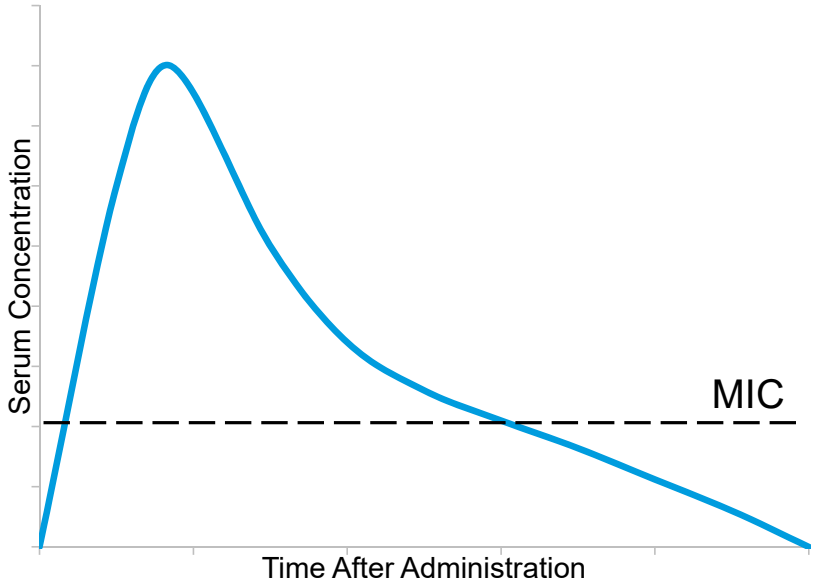
Open response

Patient Case

Our patient has symptoms consistent with her previous UTIs. She has a culture history of *Enterobacter* and *Pseudomonas*, so she is started on cefepime 1g every 12 hours because of a presumed AKI.

Beta-Lactam Pharmacodynamics

- Pharmacokinetics intimately linked to antibiotic pharmacodynamics



Eagle H, et al. *N Engl J Med*. 1953;248:481-88.
Turnidge JD. *Clin Infect Dis*. 1998;27:10-22.

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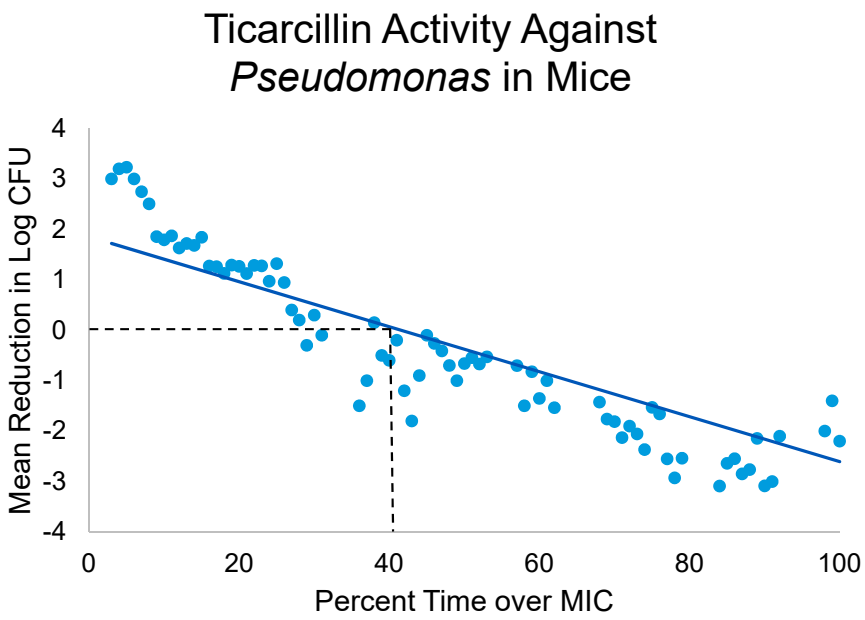
Beta-Lactam Pharmacodynamics and Pharmacokinetics

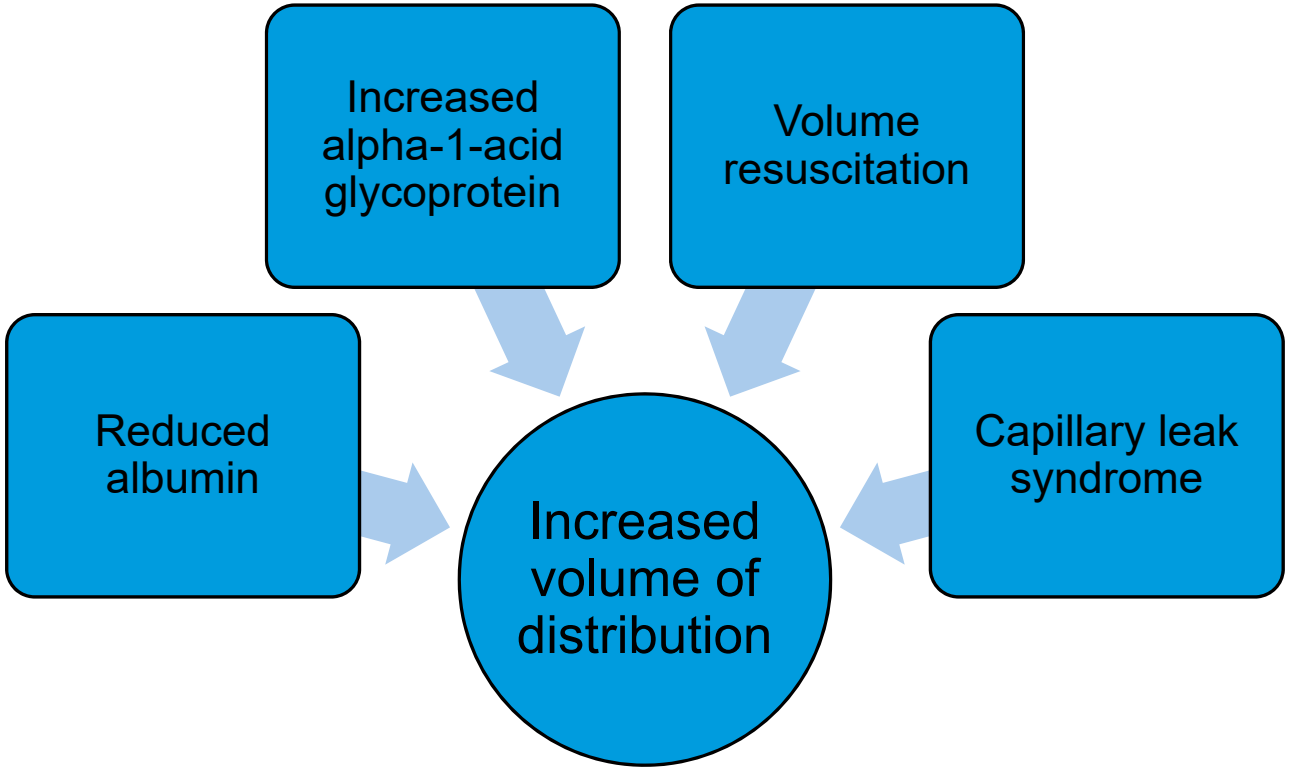
- Time over MIC explains 81% of the variation in CFU reduction in mice
- Longer time over MIC, more bacterial killing

40% time over MIC often chosen because it is near the inflection point where bacteria no longer grow



Vogelman B, et al. *J Infect Dis*. 1988;158:831-47

Distribution Changes in Critical illness



Other factors:

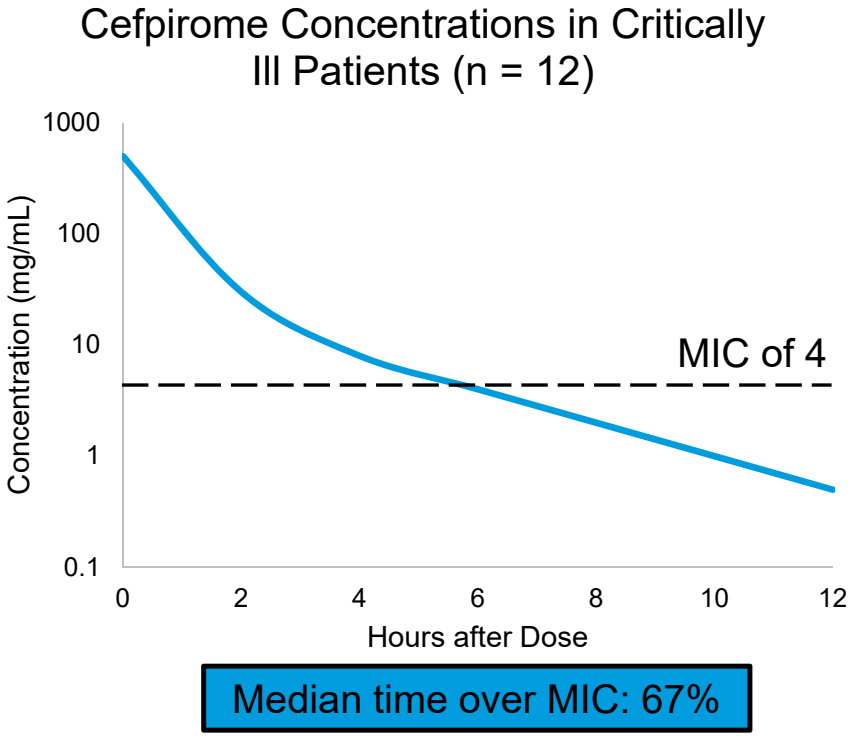
- Obesity
- ECMO
- Cystic fibrosis

Smith BS, et al. *Chest*. 2012;141:1327-36.

Distribution Changes in Critical illness

- Beta-lactams are hydrophilic and are susceptible to V_D expansion
- Pharmacokinetics of cefpirome evaluated at steady state in 12 critically ill patients

	Parameters in Healthy Adults	Parameters in Critical Illness
Half-Life	2 hours	2.5 hours
Volume of Distribution	15-17 L	24 L

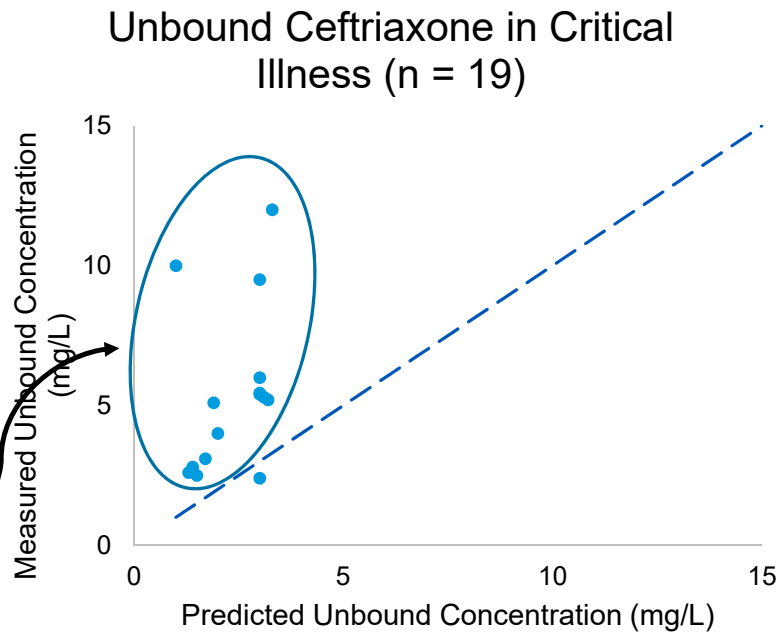


Lipman J, et al. *Intensive Care Med*. 2001;27:363-70.

Protein Binding

- Many beta lactams are not heavily protein bound
  - Ceftriaxone (~90%) and cefazolin (~80%) are exceptions
- Only unbound drug is active
  - Unpredictable in critical illness for some agents

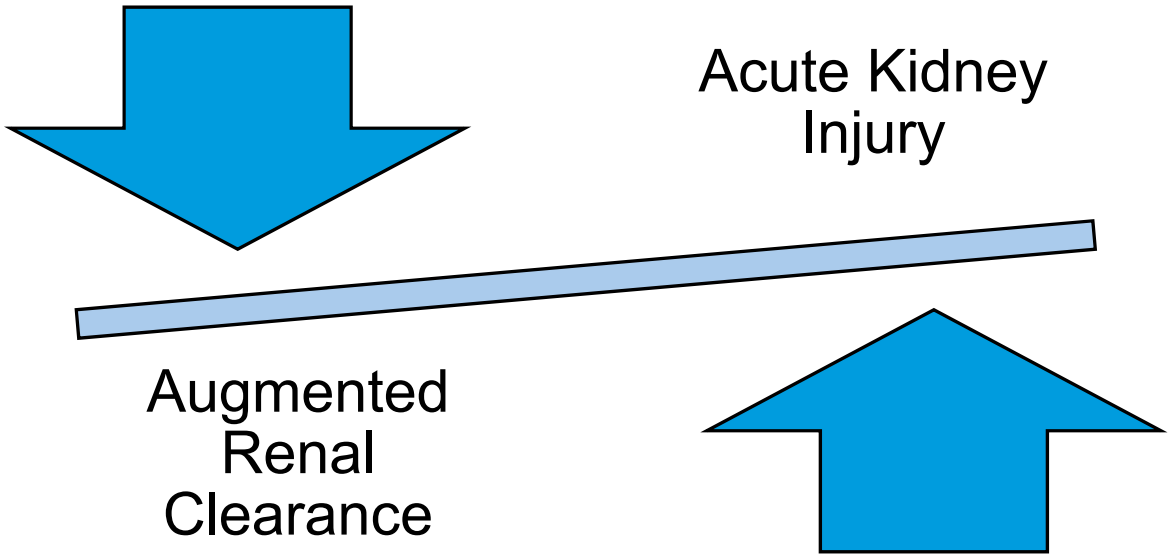
Actual unbound concentrations significantly higher than predicted



Wong G, et al. *Antimicrob Agent Chemother*. 2013;57:6165-70.

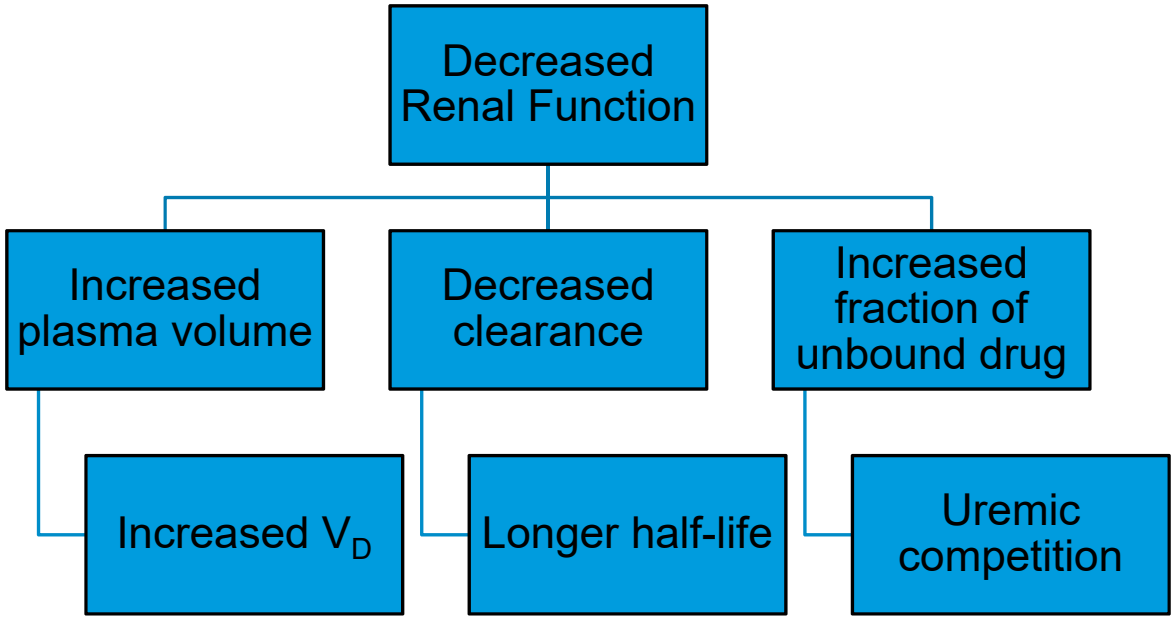
Excretion Changes in Critical Illness

- Beta lactams are most often renally eliminated
  - Ceftriaxone exception here



Renal Failure

- Around 30% of ICU patients experience AKI



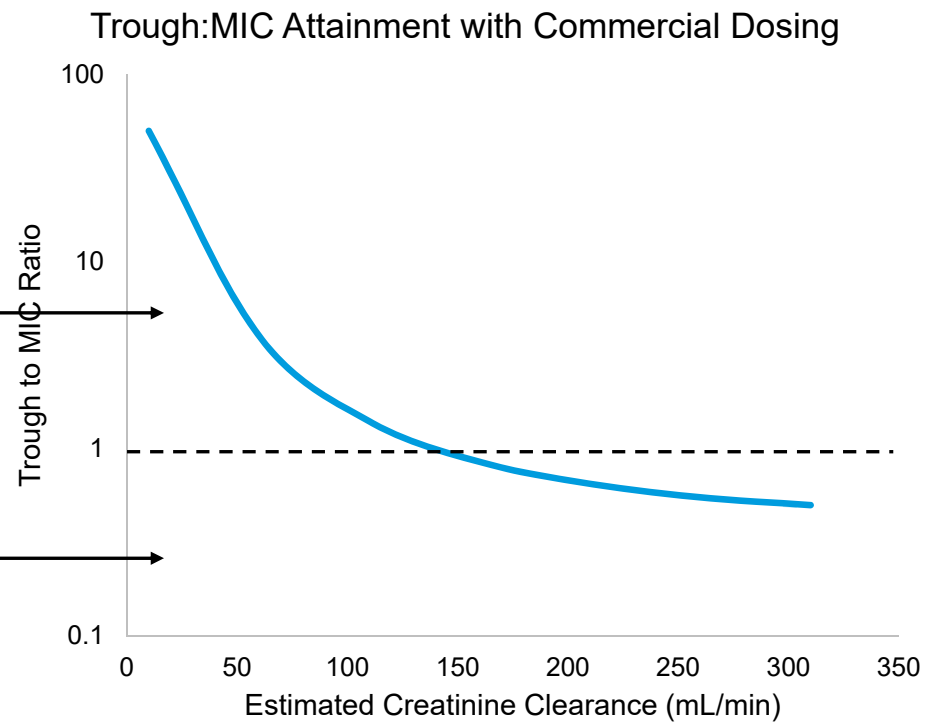
Joannidis M, et al. *Intensive Care Med*. 2009;35:1692-1702.

Augmented Renal Clearance

- Faster clearance directly correlated with failure to achieve a trough level above the MIC

Values above 1 represent troughs above the MIC of a cultured organism

Values below 1 represent troughs below the MIC of a cultured organism



Udy AA, et al. *Chest*. 2012;142:30-9.

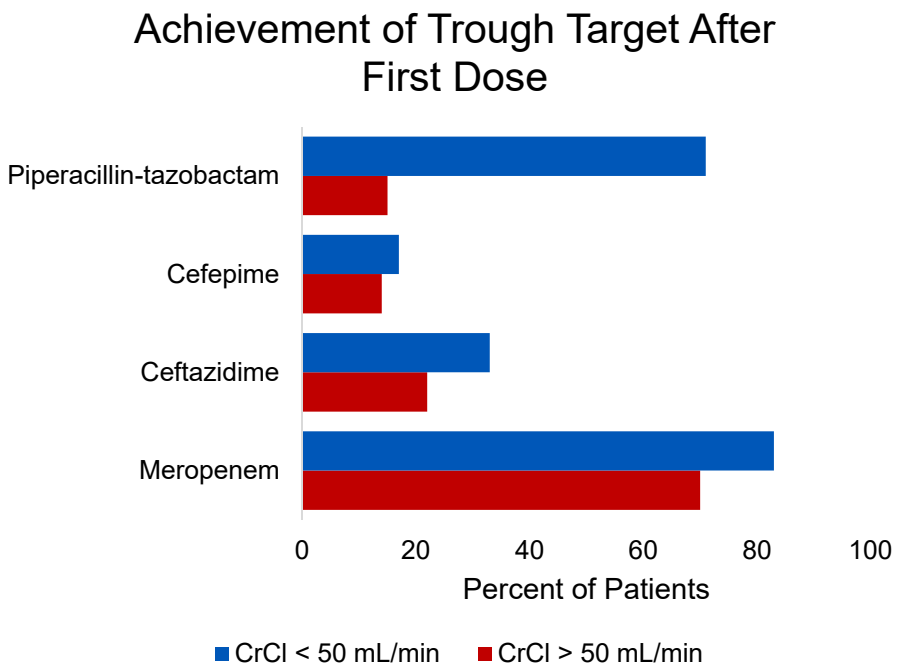
Assessment Question #1

On day 2 of therapy, our patient experiences worsening AKI with creatinine doubling overnight. Which of the following PK changes may occur in response to this?

- Decreased elimination
- Increased volume of distribution
- Increased exposure
- All of the above

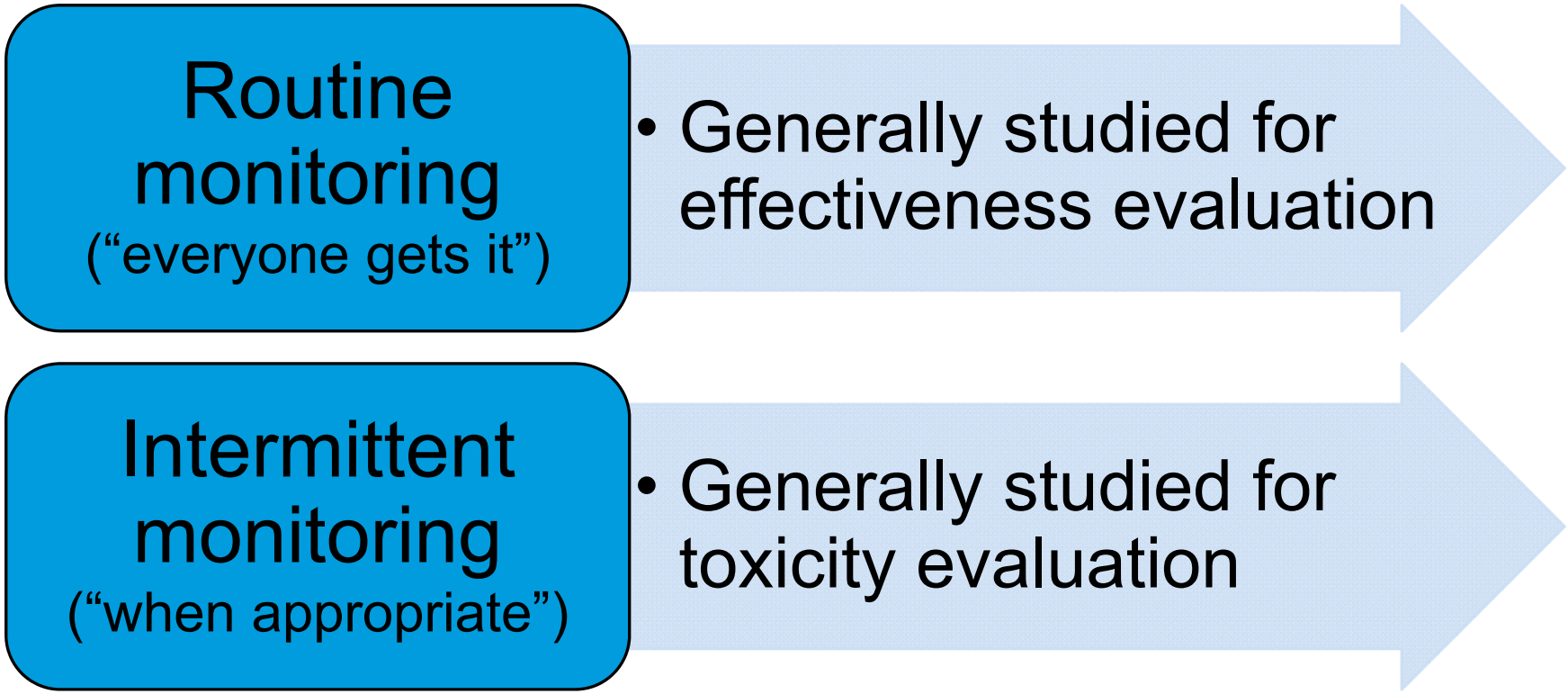
Rationale for Beta Lactam Monitoring

- Many patients do not achieve target with commercial dosing
- 80 critically ill patients had serial levels drawn after first dose adjusted for renal function
- Failing to hit targets early may promote resistance and decrease chance of cure

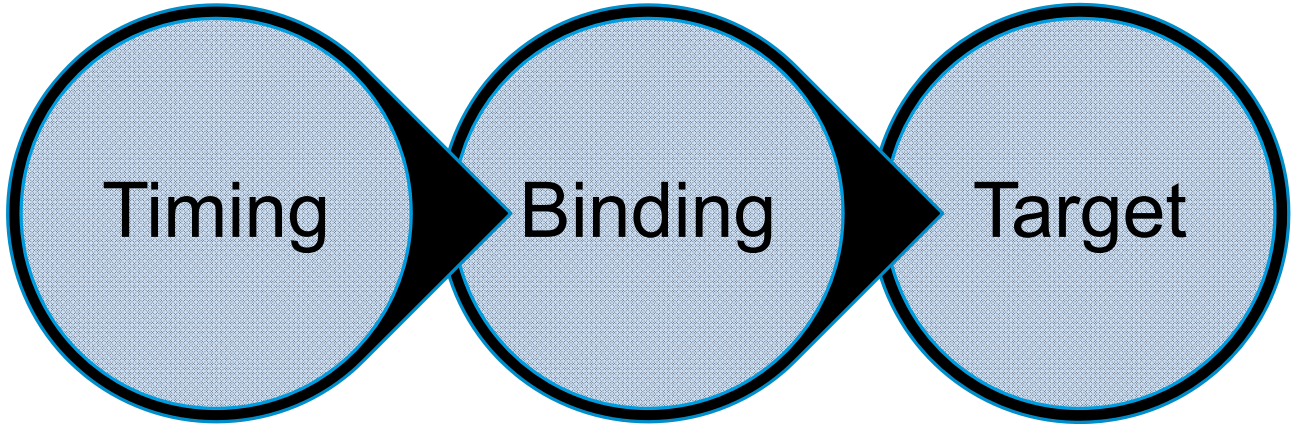


Taccone FS, et al. *Crit Care*. 2010;14:R126.
Bergen PJ, et al. *J Antimicrob Chemother*. 2016;71:25009-2520.

Should we Use TDM?



Additional Considerations



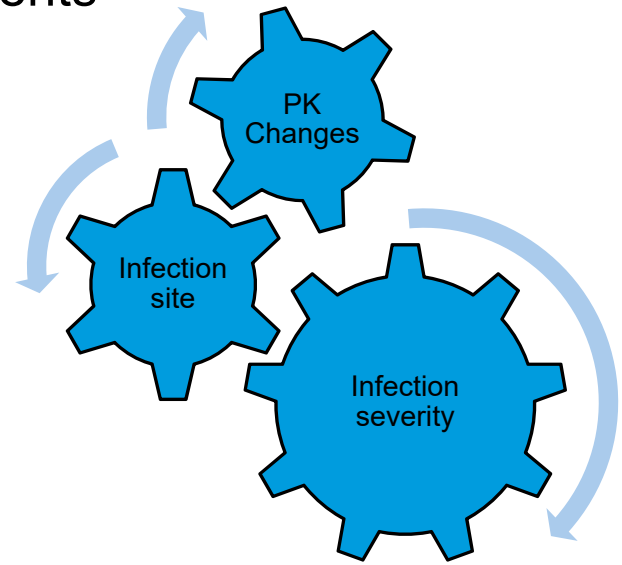
- Currently send-out lab at Mayo
- Generally only total drug available
- Assumed MIC for pending or negative cultures

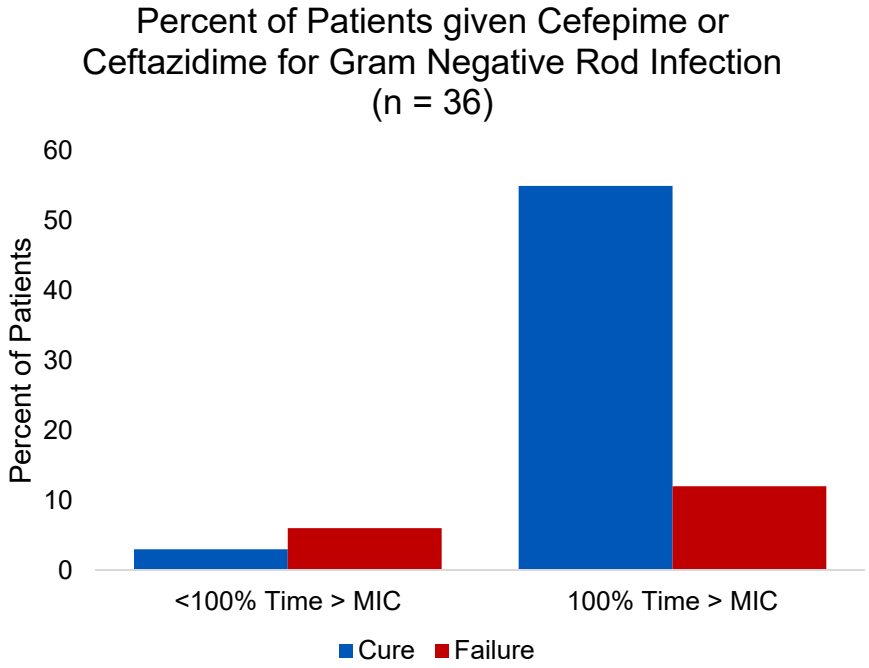
Cefepime	Piperacillin	Ceftriaxone	Meropenem
4 mg/L	16 mg/L	1 mg/L	2 mg/L

Wong G, et al. *J Antimicrob Chemother.* 2014;69:1416-23.

Targets: Is 40% Time > MIC Enough?

- 40% may not be sufficient for some patients

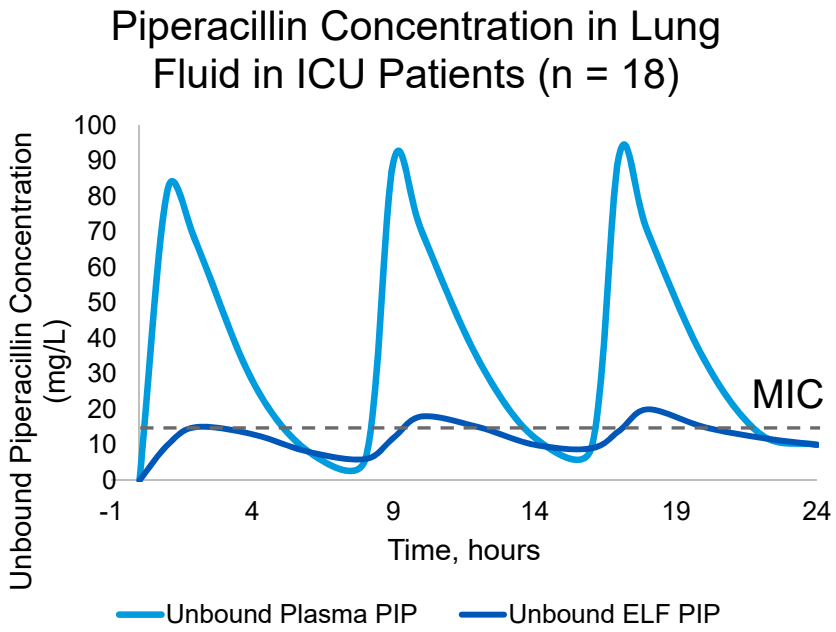




Tam VH, et al. *J Antimicrob Chemother*. 2002;50:425-8.
McKinnon PS, et al. *Int J Antimicrob Agents*. 2008;31:345-51.

Sites of Infection: Do they Matter?

- Blood samples not representative of levels in all organs
  - CNS
  - Lung
  - Prostate
  - Bone
- Underscores importance of overshooting MIC target

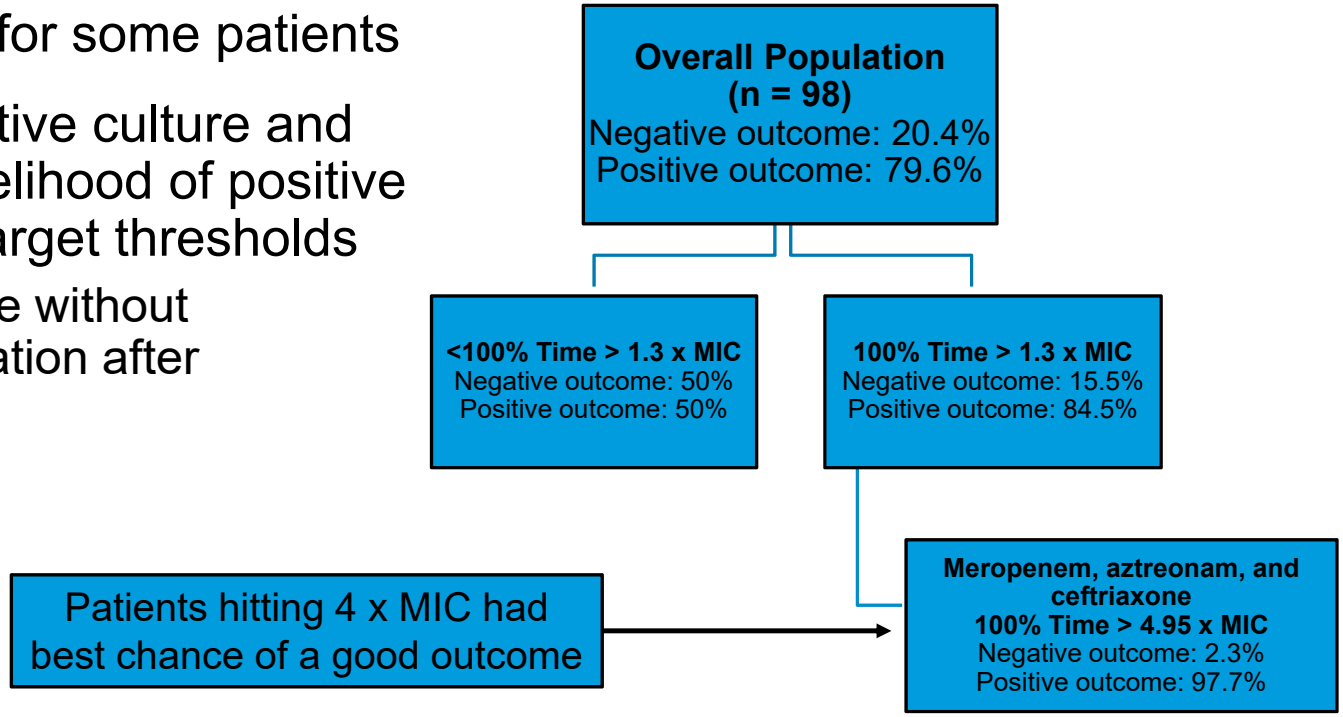


ELF: epithelial lining fluid
PIP: piperacillin

Felton TW, et al. *Clin Pharmacol Ther*. 2014;96:438-48.

Thresholds for Adjustment

- 4 x MIC may be ideal for some patients
- ICU patients with positive culture and TDM evaluated for likelihood of positive outcome at different target thresholds
  - Completion of course without escalation or re-initiation after discontinuation



Wong G, et al. *J Antimicrob Chemother*. 2020;75:429-33.

Quantification of PK Attainment in ICU Patients

- At steady state, most agents also fail to meet aggressive PK targets

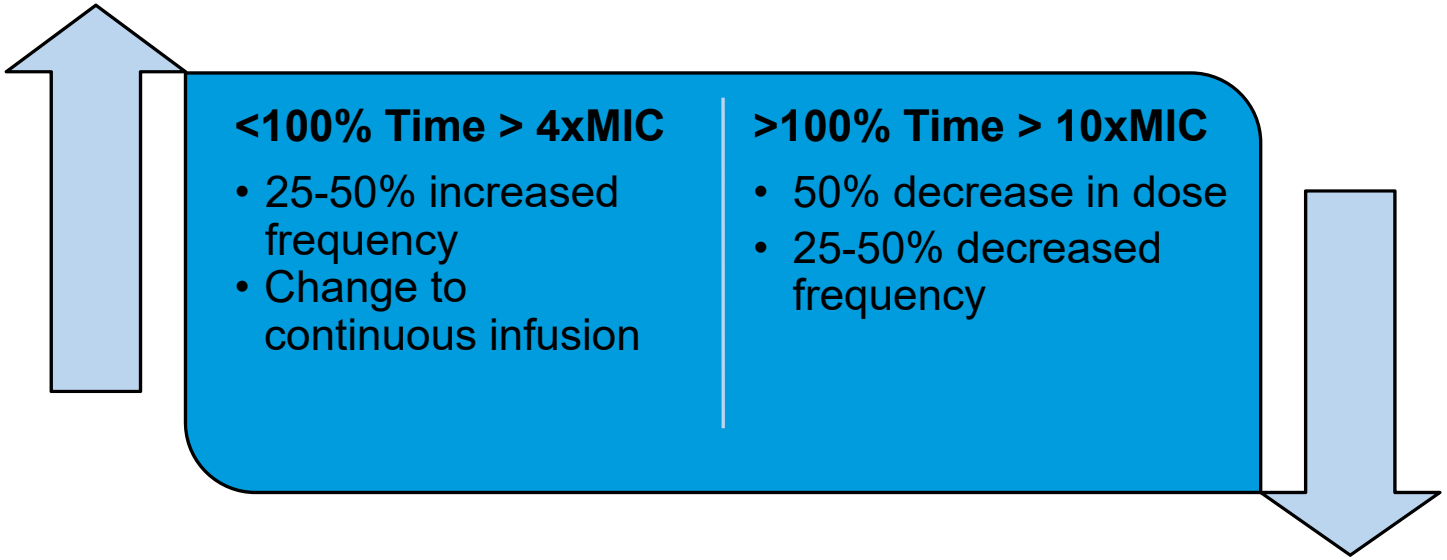
Unbound Concentrations	**Cefepime (n = 14)**	**Ceftriaxone (n = 33)**	**Piperacillin (n = 109)**	**Meropenem (n = 89)**
50% Time > MIC	78.6%	97.0%	80.6%	95.0%
50% Time > 4x MIC	50.0%	93.9%	48.9%	68.8%
100% Time > 4x MIC	**71.4%**	**87.9%**	**30.3%**	**41.6%**
Mean daily dose	6 g	2 g	12 g	3 g

- Patients failing to meet minimum of 50% T > MIC had worse outcomes
  - OR for clinical failure 1.47, 95% CI 1.09, 1.92

Roberts JA, et al. *Clin Infect Dis*. 2014;58:1072-83.

Dose Adjusting using TDM

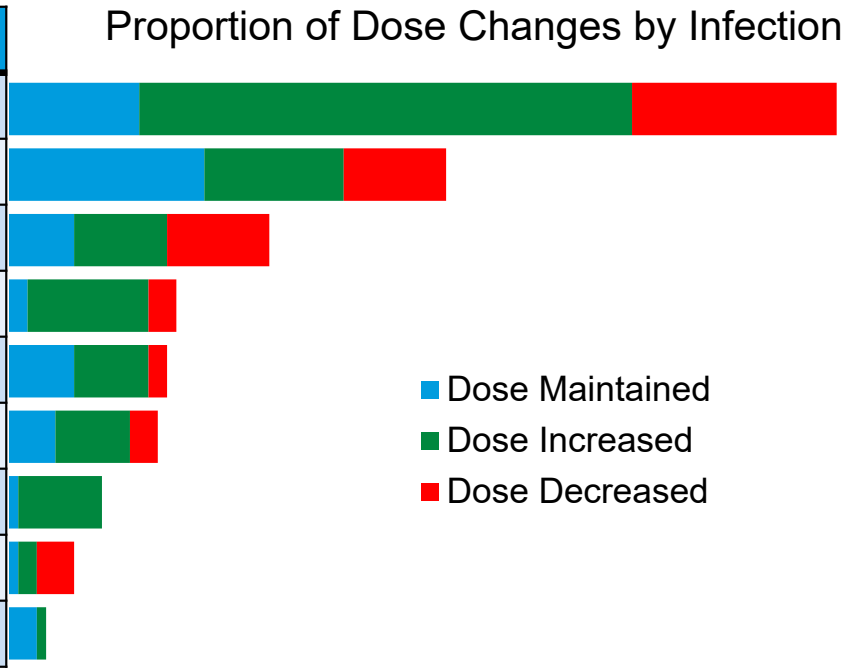
- Protocolized beta-lactam monitoring and dose adjusting implemented in ICU population



Roberts JA, et al. *Int J Antimicrob Agent*. 2010;36:332-9.

Dose Adjusting using TDM

Infection Type	Population (n = 236)
HAP	38%
CAP	20%
Abdominal Infection	12%
Bacteremia	8%
Meningitis	7%
ABSSSI	7%
Prophylaxis	4%
UTI	3%
Neutropenic Fever	2%

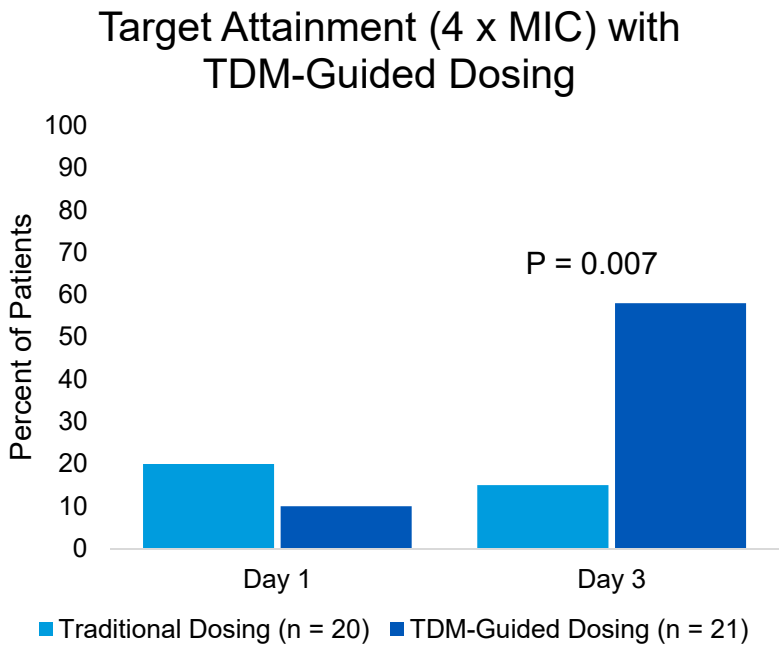


87.3% deemed a positive clinical outcome

Roberts JA, et al. *Int J Antimicrob Agent*. 2010;36:332-9.

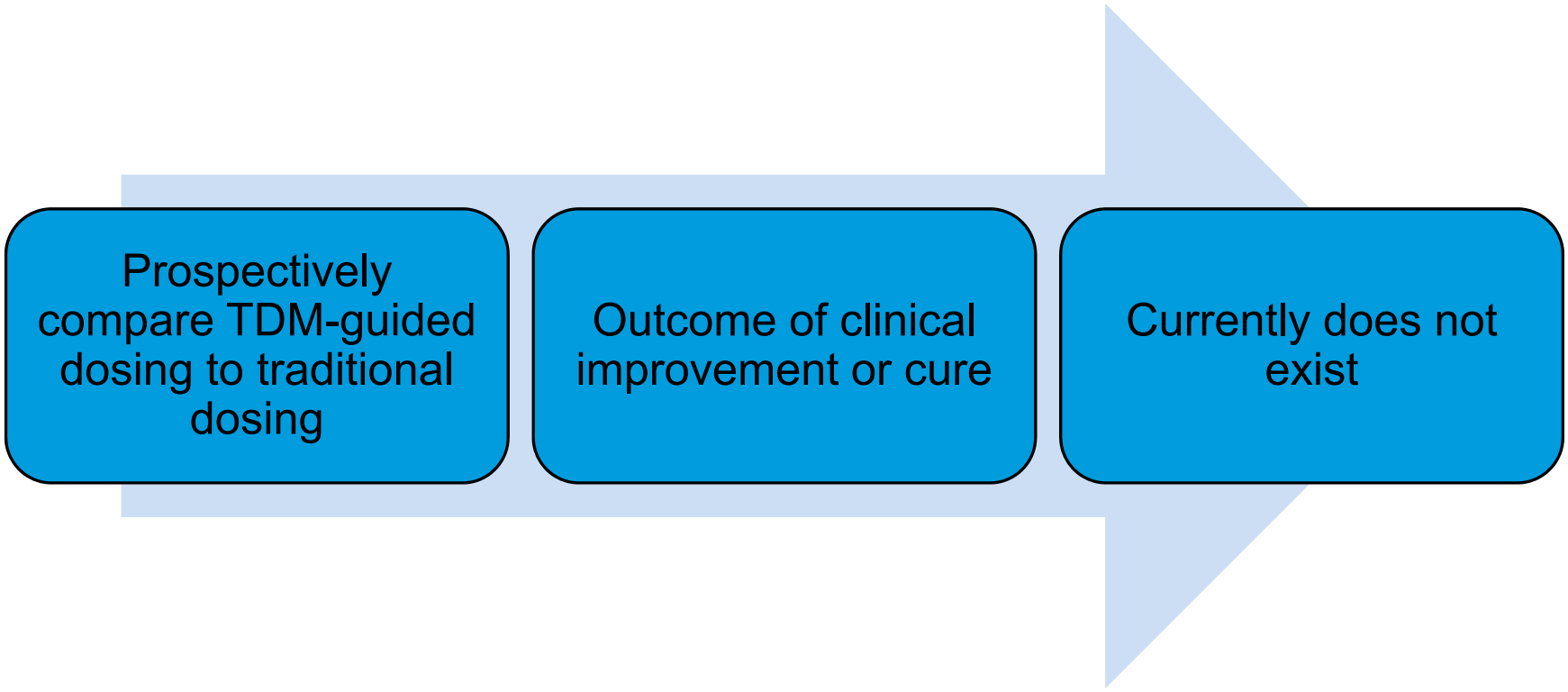
Is Better than Traditional Dosing?

- ICU patients randomized to TDM-guided and conventional dosing
- TDM-guided dosing led to adjustments in 76% of patients
- Persistently positive cultures in 5 traditionally dosed patients and 1 TDM-guided patient at day 7
- Concordant data exist for febrile neutropenia and pediatrics

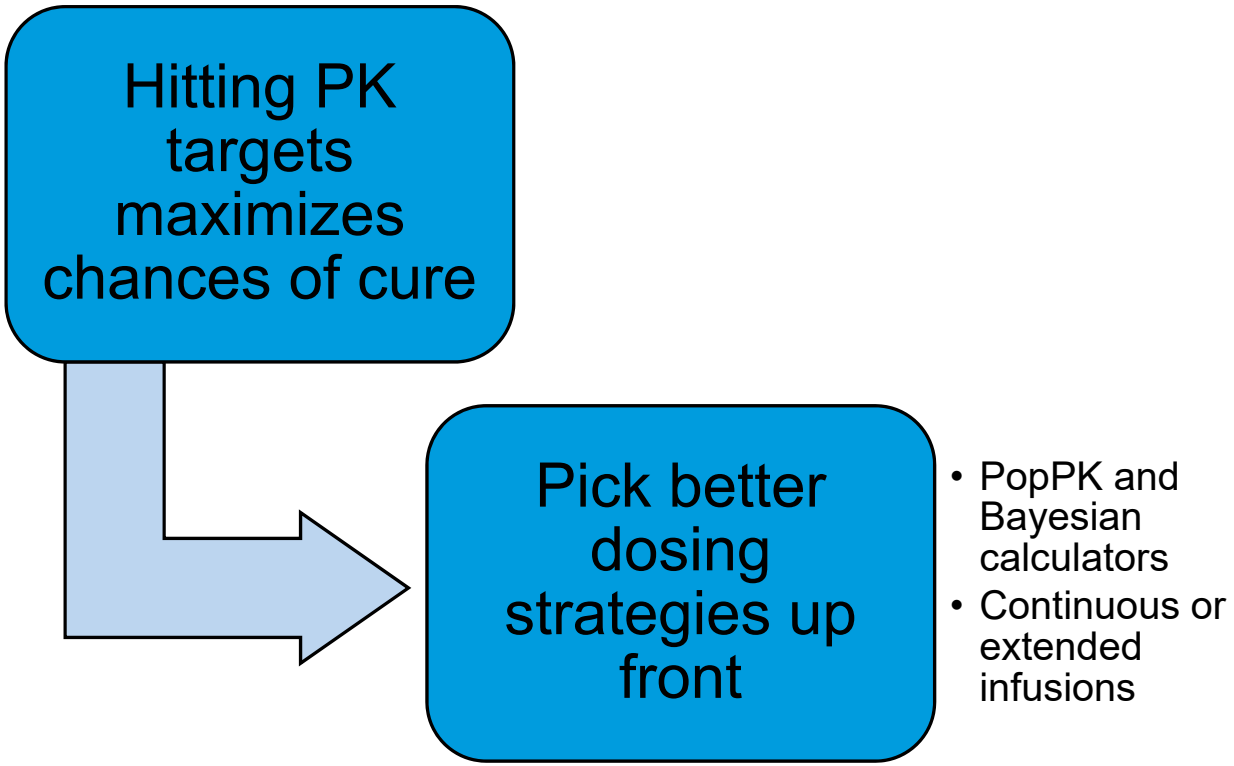


De Waele JJ, et al. *Intensive Care Med.* 2013;40:380-87.

Ideal Trial

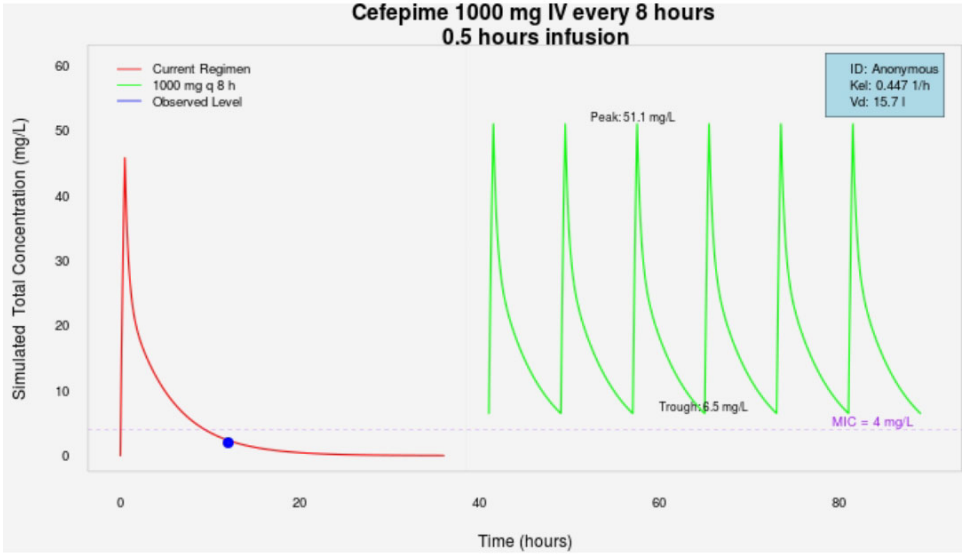

Prospectively compare TDM-guided dosing to traditional dosing
Outcome of clinical improvement or cure
Currently does not exist

What we Know


Hitting PK targets maximizes chances of cure
Pick better dosing strategies up front
• PopPK and Bayesian calculators
• Continuous or extended infusions

Bayesian Prediction

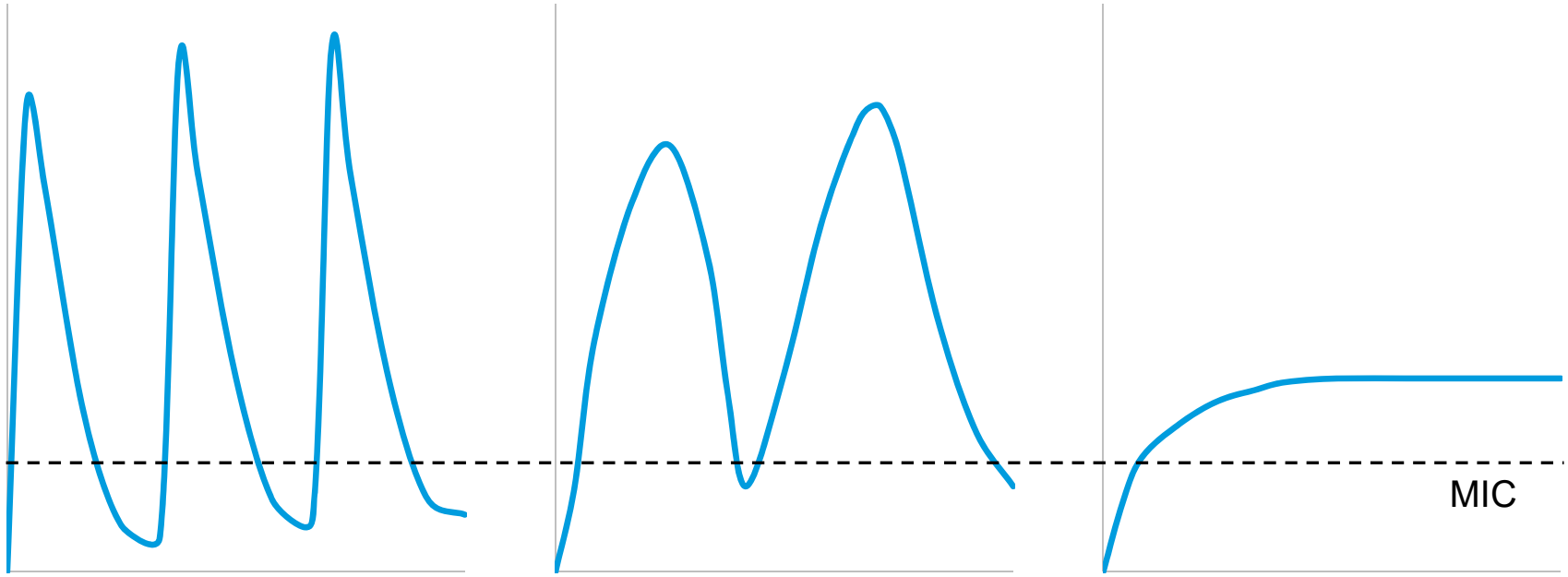
- Monte-Carlo predictions can be used to calculate ideal dose
- Using ID-ODS app led to 22% of patients receiving doses different from package insert recommendation
- Using our patient's data
  - 82 years old
  - SCr of 2.2 mg/dL
  - Cefepime 1g q12
  - Trough of 2 mg/L



Heil EL, et al. *Antimicrob Agent Chemother*. 2018;62:e01008-18.

Continuous or Extended Infusion

Intermittent Bolus (IB) • Extended Infusion (EI) • Continuous Infusion (CI)



BLING II Trial

ICU Patients
Continuous infusion
Intermittent Bolus

Daily dose:
13.5g (piperacillin/tazobactam),
3.0g (meropenem),
12.4g (ticarcillin/clavulanate)

	Continuous (n = 219)	Intermittent (n = 224)	P-Value
Primary Outcome			
ICU-Free Days	18	20	0.38
Secondary Outcomes			
90-Day Mortality	25.7%	27.5%	0.67
14-day Cure	52.4%	49.%	0.56

- Low number of positive cultures and low cure rate overall
- Short antibiotic duration
- No PK data
- 25% of patients required RRT

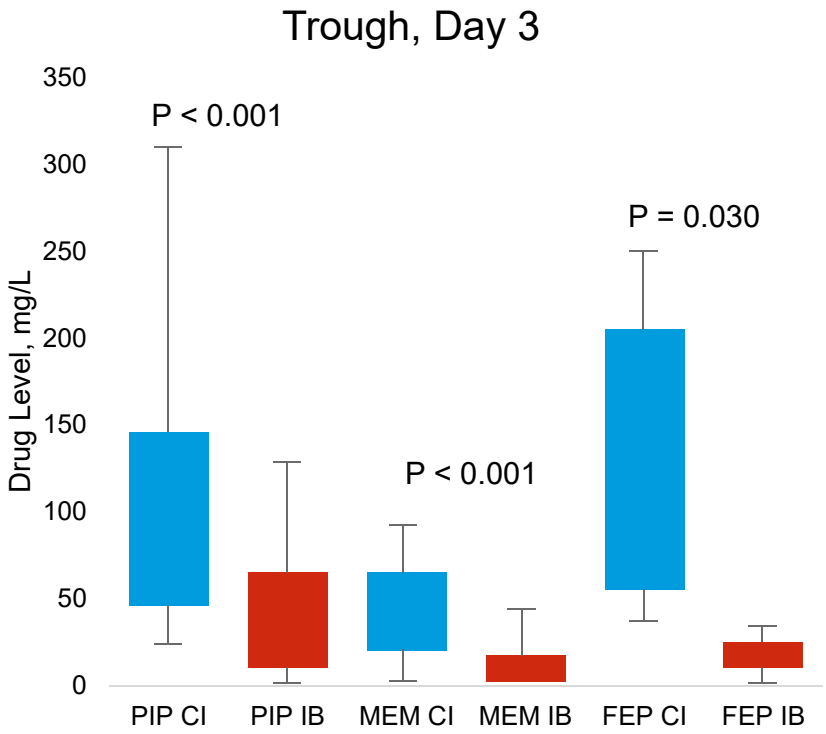
Dulhunty JM, et al. *Am J Respir Crit Care Med*. 2015;192:1298-305.

BLISS Trial

ICU Patients
Continuous infusion
Intermittent Bolus

Daily dose:
18g (pip/tazo),
3.0g (meropenem),
6g (cefepime)

	Continuous (n = 70)	Intermittent (n = 70)	P-Value
Primary Outcome			
14-day Cure	56%	34%	0.011
Secondary Outcomes			
T > MIC	97%	68%	<0.001
ICU Free Days	20	17	0.378
30-Day Mortality	26%	37%	0.145



PIP: piperacillin, MEM: meropenem, FEP: cefepime
CI: continuous infusion, IB: intermittent bolus

Abdul-Aziz MH, et al. *Intensive Care Med*. 2016;42:1535-45.

Future Directions

DOLPHIN

- ICU patients randomized to TDM-guided dosing or traditional dosing
- Primary outcome: ICU length of stay

TARGET

- Patients with sepsis randomized to CI TZP with daily TDM or CI TZP without TDM
- Primary outcome: Change in SOFA score at day 10

BLING IIII

- Patients with sepsis randomized to CI or IB beta-lactam
- Targeting enrollment of 7,000 patients
- Primary outcome: 90-day mortality

CI: continuous infusion
IB: intermittent bolus
TZP: piperacillin-tazobactam

Abdulla A, et al. *BMC Infect Dis*. 2020;20:57.
Hale S, et al. *Trials*. 2019;20:330.
Lipman J, et al. *Crit Care Resusc*. 2019;21:63-8.

Operational Considerations

In patients deemed to benefit from TDM

Clear PK alternation (AKI, ARC, etc) or risk of poor outcome (high MIC)

Draw steady state trough sample	Can use total level for most beta-lactams and extrapolate unbound	Target 100% above MIC and ideally 100% 4 x MIC • If no MIC yet, assume highest MIC breakpoint

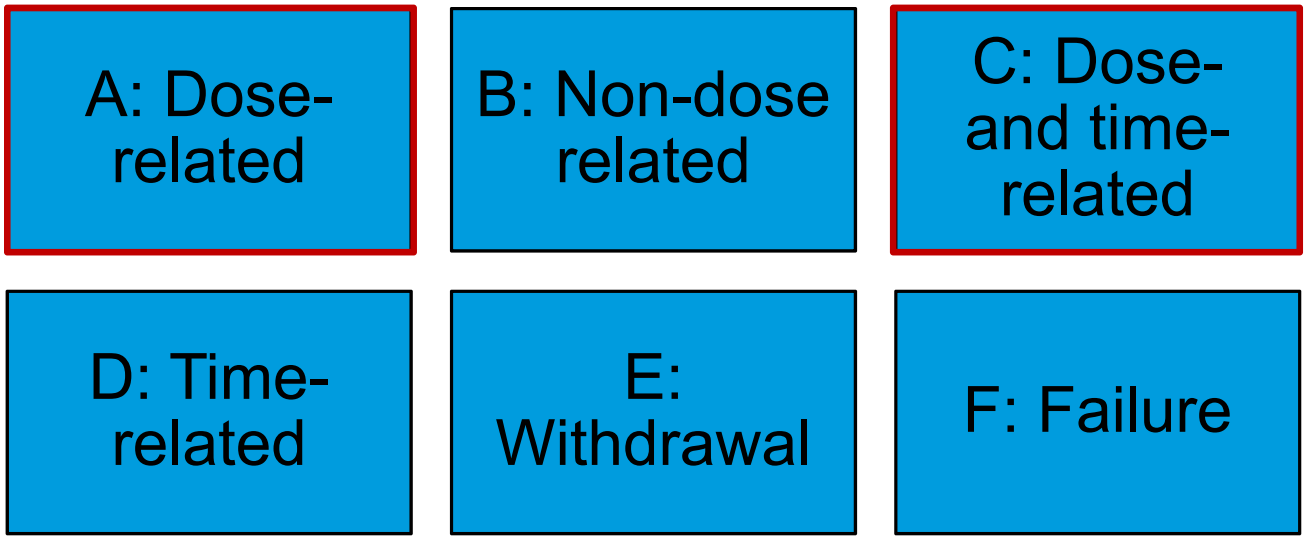
Assessment Question #2

Our patient's urine speciates *Acinetobacter baumanii*. Cefepime's MIC for the organism is 4 mg/L. She begins to decline, and the treating team changes the cefepime to continuous infusion and checks a level after 24 hours. What is your goal level?

- 4 mg/L
- 5.2 mg/L
- 100 mg/L
- 16 mg/L

Types of Adverse Drug Reactions

- Not all adverse drug reactions are created equal



Focus will be on neuro and nephrotoxicity

Edwards IR, et al. *Lancet*. 2000;7:356:1255-9.

Neurotoxicity

- Beta-lactams long known to be neurotoxic
  - Lumbar injection of penicillin G caused significant paresthesia in monkeys
  - Intracortical injection of penicillin G into mice caused myoclonic seizure
- Believed to antagonize unique binding site at $GABA_A$ channel

Mouse EEG Tracing Without Penicillin

Mouse EEG Tracing After 500 IU Intracortical Penicillin

Walker A, et al. *Ann Surgery*. 1945;122:1125-35.
Akodgan I, et al. *Brain Res Bull*. 2008;

Neurotoxicity Symptoms

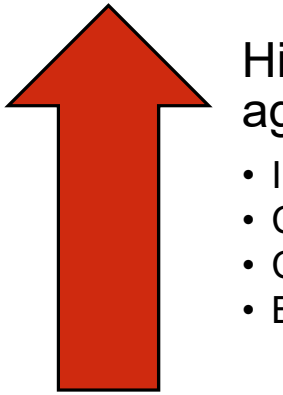
Seizures

- NCSE
- Myoclonus
- Cerebellar spasm

Psychosis

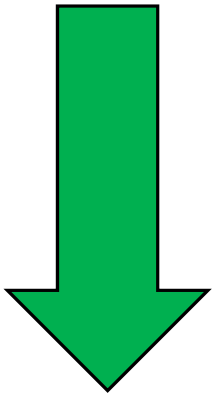
- Difficult to differentiate from delirium

EEG abnormalities



High risk agents

- Imipenem
- Cefepime
- Cefazolin
- Benzylpenicillin



Moderate risk agents

- Ceftriaxone
- Piperacillin

Battacharrya S, et al. *Neurology*. 2016;86:963-71.
De Sarro A, et al. *Antimicrob Agent Chemother*. 1995;39:232-7.
Day IP, et al. *Tox Letters*. 1995;76:239-43.

Need to Appropriately Dose

- Clinical findings of neurotoxicity most often reported in patients with renal dysfunction inappropriately dosed

Age	Daily Cefepime Dose	Creatinine at Seizure	Cefepime Trough
16	9 g	10.6 mg/dL	134 mg/L
73	4 g	2.1 mg/dL	73 mg/L
65	2 g	3.2 mg/dL	Not measured
73	2 g	4.3 mg/dL	72 mg/L

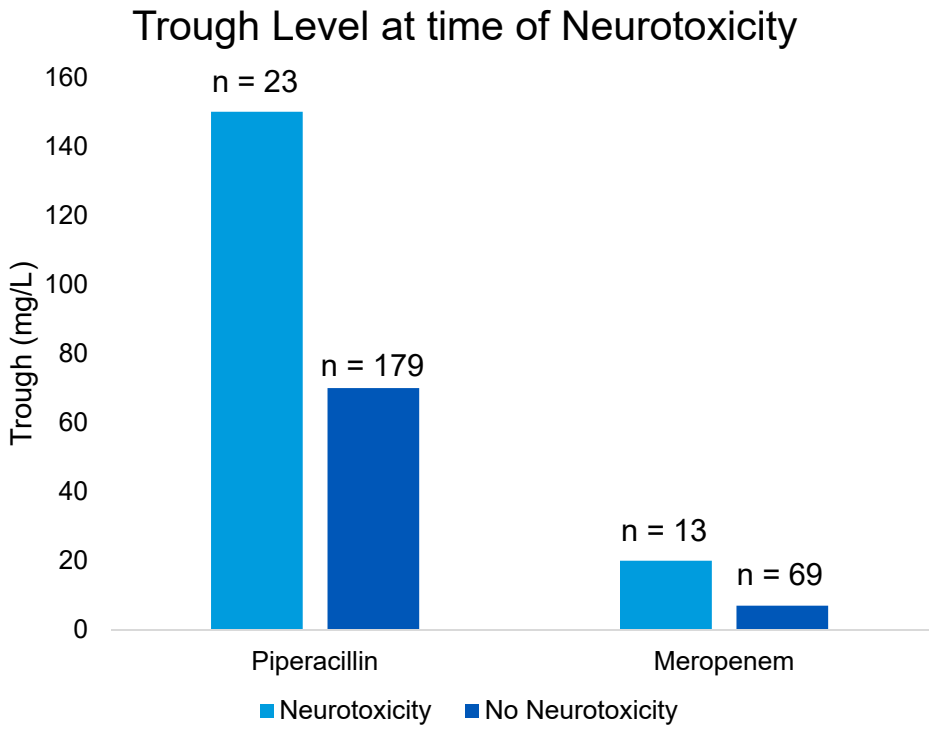
- CSF penetration increases with higher peaks, meningeal inflammation, and uremic competition at CNS export proteins

Chatellier D, et al. *Intensive Care Med*. 2002;28:214-7.
Nau R, et al. *Clin Microbiol Rev*. 2010;23:858-83.

Neurotoxicity Associated with Higher Trough

- Retrospective analysis of all patients with beta-lactam TDM
- Neurotoxicity defined by:
  - Declining GCS
  - Abnormal EEG
  - Symptoms of neurotoxicity
  - Unexplained by other cause

Treatment with benzodiazepine protective of neurotoxicity for piperacillin
OR 0.26 (95% CI 0.07, 0.96)



Imani S, et al. *J Antimicrob Chemother*. 2017;72:2891-97.

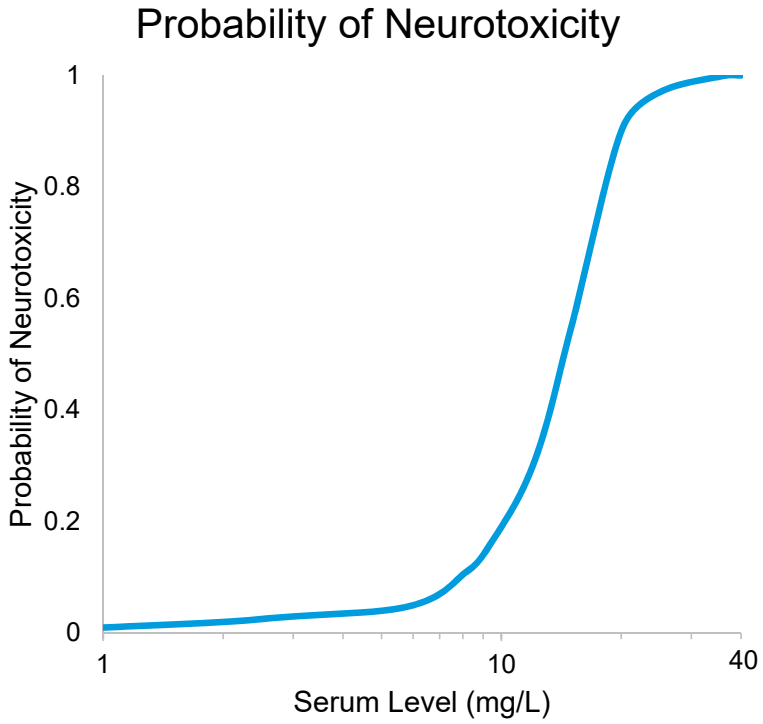
Practical Role of Monitoring

- Levels at the extremes have good predictive value for neurotoxicity
- Retrospective analysis of 74 patients with cefepime TDM

Cefepime trough <7.7 mg/L
0% neurotoxicity

Cefepime trough >38.1 mg/L
100% neurotoxicity

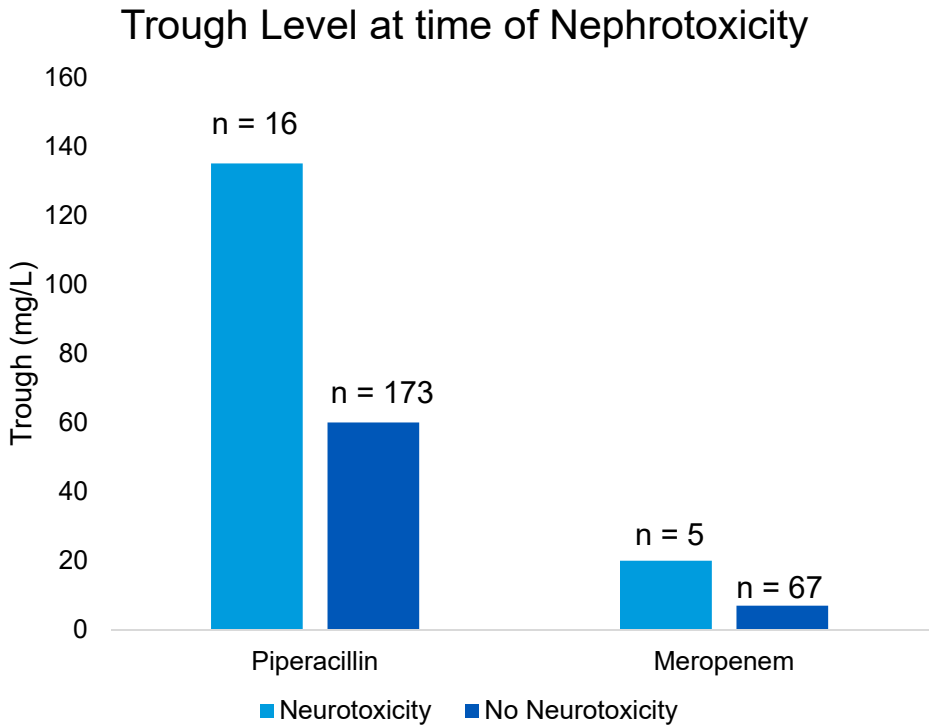
Checking level may have role in ruling in or out a suspected case of neurotoxicity



Boschung-Pasquier L, et al. *Clin Microbiol Infect*. 2020;26:333-9.

Nephrotoxicity Associated with Higher Troughs

- Retrospective analysis of all patients with beta-lactam TDM
- AKI defined by AKIN staging
- High levels may cause or be caused by AKI



Imani S, et al. *J Antimicrob Chemother*. 2017;72:2891-97.

Extended Exposure and AKI Risk

- Prolonged exposure to high levels may contribute to risk of AKI
- Retrospective analysis of 2,390 patients who received at least 48 hours of piperacillin-tazobactam, cefepime, or meropenem
  - 690 received extended infusion
  - 1,700 received intermittent infusion
- Piperacillin-tazobactam associated with higher risk regardless of infusion strategy

	Extended	Intermittent	P-Value
AKI Incidence	21.6%	18.6%	0.104

	OR for AKI	95% CI
Cefepime	*Reference*	
Meropenem	1.04	0.73, 1.48
Piperacillin-tazobactam	1.95	1.50, 2.52

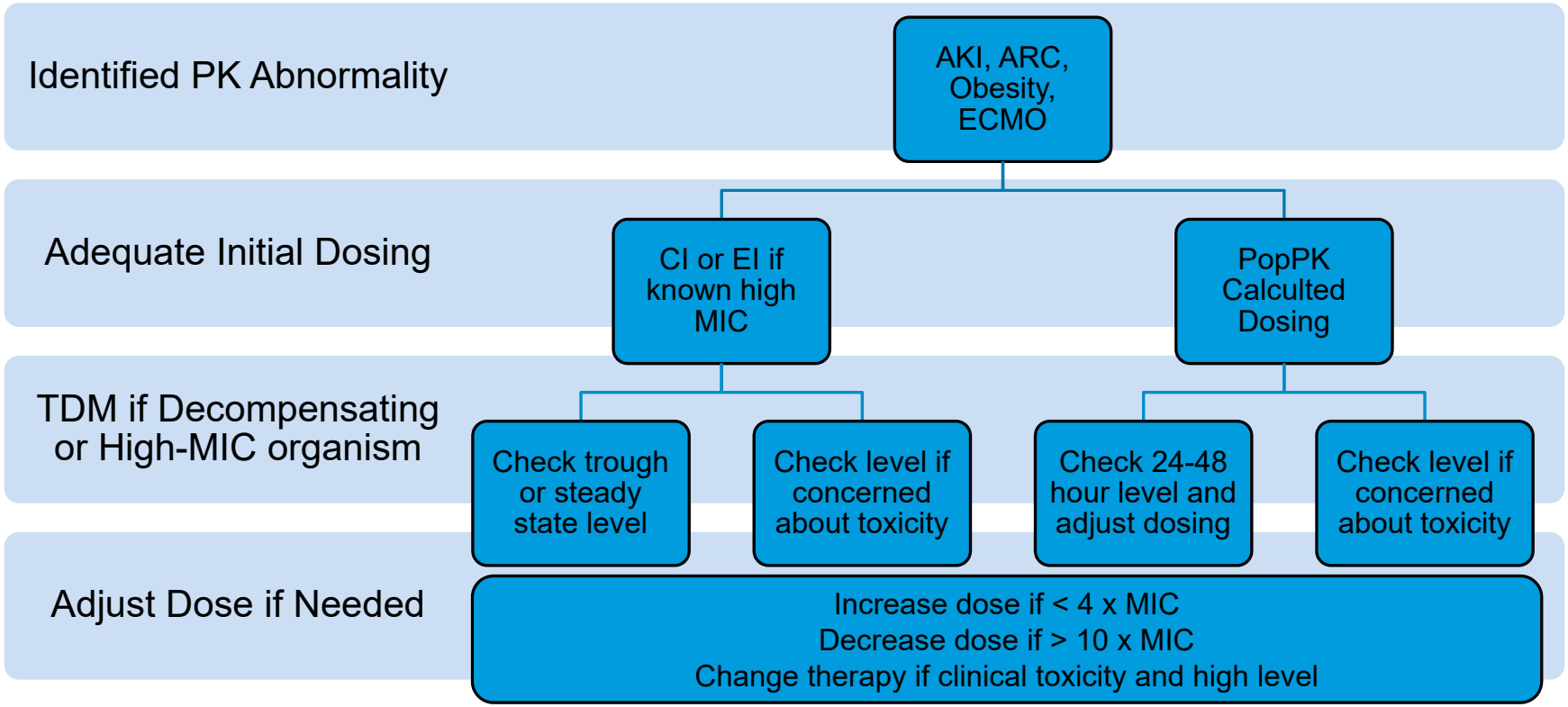
Cotner SE, et al. *Antimicrob Agent Chemother*. 2017;61:e00871-17.

Assessment Question #3

Our patient with *A. baumanii* UTI was clinically improving but became alerted and suffered from a seizure after 3 days on continuous cefepime. A level is checked and is 6 mg/dL (MIC of 4 mg/dL). What is the best action to take?

- Decrease the dose to a target of level of 3 mg/L
- Increase the dose to a target level of 20 mg/L
- Switch to piperacillin/tazobactam
- Investigate other causes of seizure

Potential TDM Flowsheet



Conclusion

- Patients with critical illness have profound changes in pharmacokinetics
- Beta-lactam therapeutic drug monitoring may have a place in select patients but routine use is not supported yet
- TDM effectiveness targets are dynamic and patient-specific
- TDM may have a role in delineating the contribution of beta-lactams to dose-related toxicity

Questions and Discussion

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