Augmented Renal Clearance: Let's Get the Discussion Flowing

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MEDICINE *of* THE HIGHEST ORDER

UR MEDICINE

Disclosures

Nothing to disclose

Pharmacist Objectives

1. Explain the concept of augmented renal clearance and review the incidence and associated risk factors

2. Describe the potential impact of augmented renal clearance on attainment of antimicrobial pharmacokinetic targets

3. Evaluate the literature regarding the impact of augmented renal clearance on clinical outcomes

Background

- Augmented renal clearance (ARC) – newly described phenomenon
- ARC literature
  - Recognition
  - Pharmacokinetics in the critically ill population
  - Clinical outcomes
- Dangers of inadequate dosing of antimicrobials in critical illness

http://www.nextavenue.org/wp-content/uploads/2015/06/Are-You-At-Risk-for-Kidney-Disease-491325253.jpg

Which of the following best describes augmented renal clearance?

A) Glomerular hypofiltration

B) Hypoperfusion of the kidneys during a shock state

C) A manifestation of enhanced renal function seen in critically ill patients

D) I'm not sure

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Augmented Renal Clearance

"Glomerular hyperfiltration"

"Enhanced renal elimination of circulating solute by the kidneys"

NO STANDARDIZED DEFINTION!

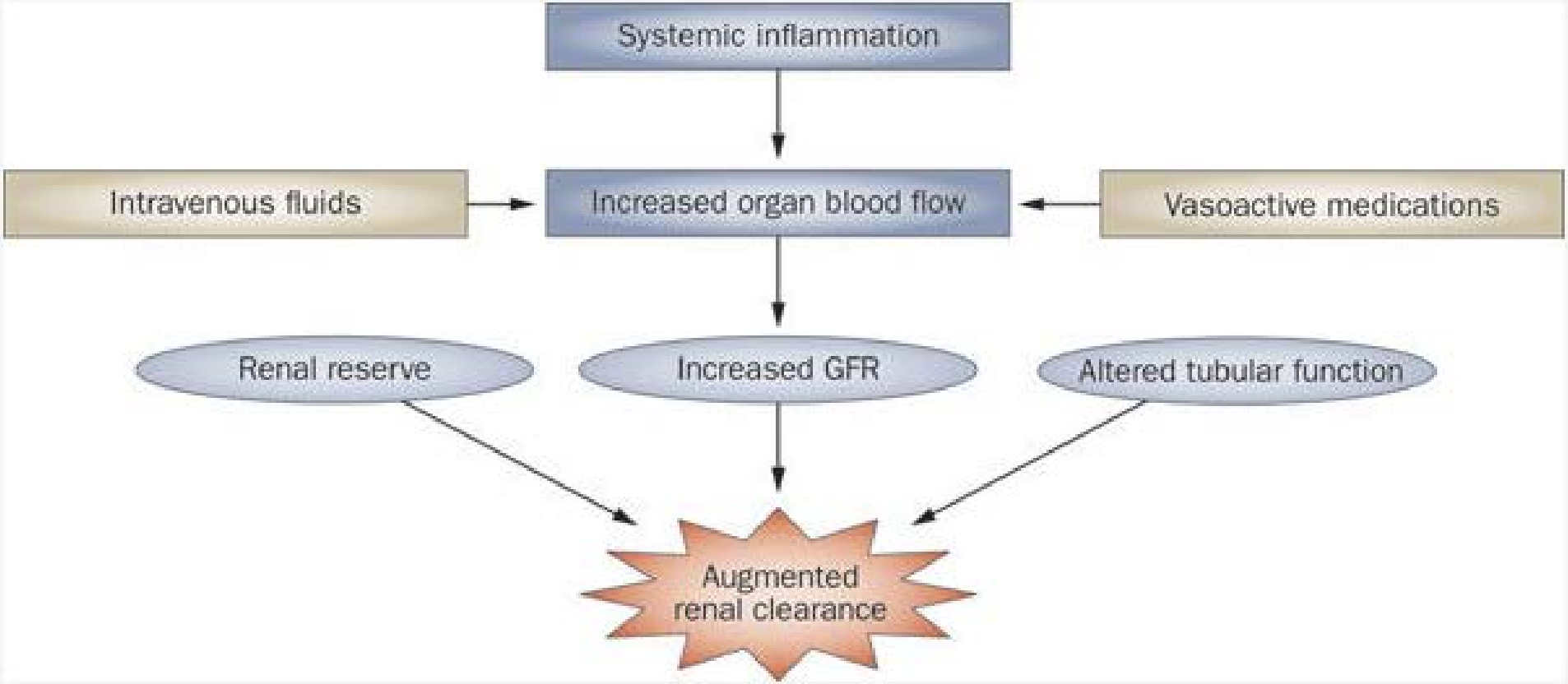
"Supraphysiologic state of kidney function"

Creatinine Clearance (CrCL)

≥ 130 mL/min/1.73m^2

Udy, et al. *Clin Pharmacokinetics* 2010;49(1):1-16; Hobbs, et al. *Pharmacotherapy* 2015;35(11):1063-1075; Udy, et al. *Nature Reviews Nephrology* 2011;7(9):539-543

Pathophysiology



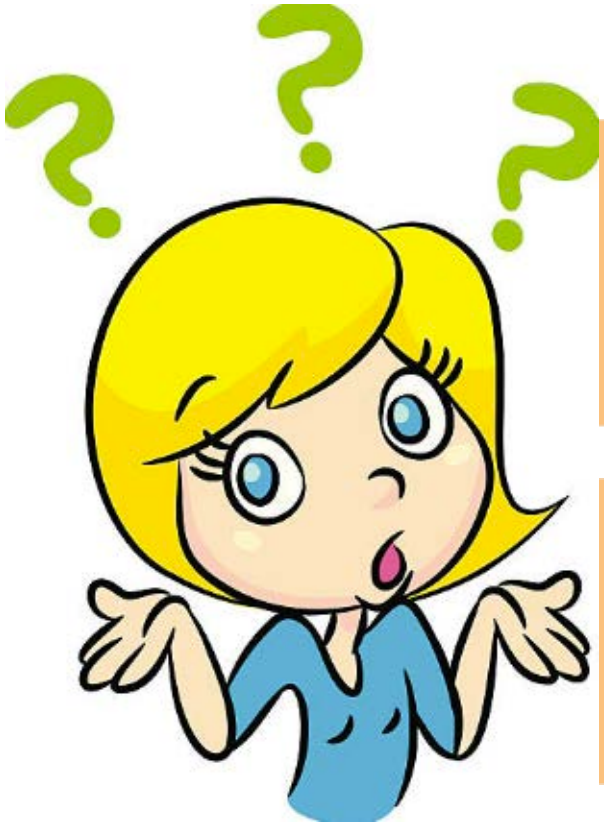
Udy, et al. *Nature Reviews Nephrology* 2011;7(9):539-543

Risk Factors

Major trauma, sepsis, burns, surgical patients

Younger age

(age < 50 years old)



Fewer comorbidities

Lower SOFA score at ICU admission

APACHE II: Acute Physiology and Chronic Health Evaluation
SOFA: Sequential Organ Failure Assessment

Udy, et al. *Clin Pharmacokinetics* 2010:49(1):1-16; Hobbs, et al. *Pharmacotherapy* 2015;35(11):1063-1075

Which of these patients is at highest risk of exhibiting ARC?

A) 80 yo F with CHF, Afib, CKD, DM2 admitted to the ICU with LLL PNA, SOFA score 15 on admission

B) 64 yo F with breast cancer admitted to the medicine service for DVT

C) 56 yo F with COPD, RA admitted to the medicine service for a rheumatoid arthritis flair

D) 25 yo M admitted to neuro-ICU with severe traumatic brain injury

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Identification of ARC

Calculated CrCL	• Cockgroft Gault (CG) • Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) • Modification of Diet in Renal Disease (MDRD)
Measured CrCL	• CrCL = Urine Cr x Volume (mL/min) / Scr • Requires 8, 12, or 24- hour urine collection

Calculated vs. Measured CrCL

Study	Methods	Results
Barletta, et al., 2016	-Calculated: CG, MDRD, CKD-EPI -Measured: 12-hr urine collection	CG & measured CrCL: r_s= 0.610 MDRD & measured CrCL: r_s= 0.547 CKD-EPI and measured CrCL: r_s= 0.595 -Weak correlation
Grootaert, et al., 2012	-Calculated: CG, MDRD -Measured: 24-hr urine collection	CG & measured CrCL: r_s= 0.343 MDRD & measured CrCL: r_s= 0.290 -Weak correlation
Ruiz et al., 2015	-Calculated: CG, MDRD, CKD-EPI -Measured: 24-hr urine collection	Bland-Altman method showed poor agreement between CG, MDRD, CKD-EPI and measured CrCL

Barletta, et al. *Journ Acute Care Surg* 2016;81(6):1115-1121; Grootaert, et al. *Ann Pharmacotherapy* 2012;46:952-9; Ruiz et al. *Annals of Intensive Care* 2015;5:49

Bottom Line

Calculated CrCL did not correlate well with measured CrCL in all of the studies

Should we measure CrCL in all patients who meet risk factors? How many risk factors?...TBD

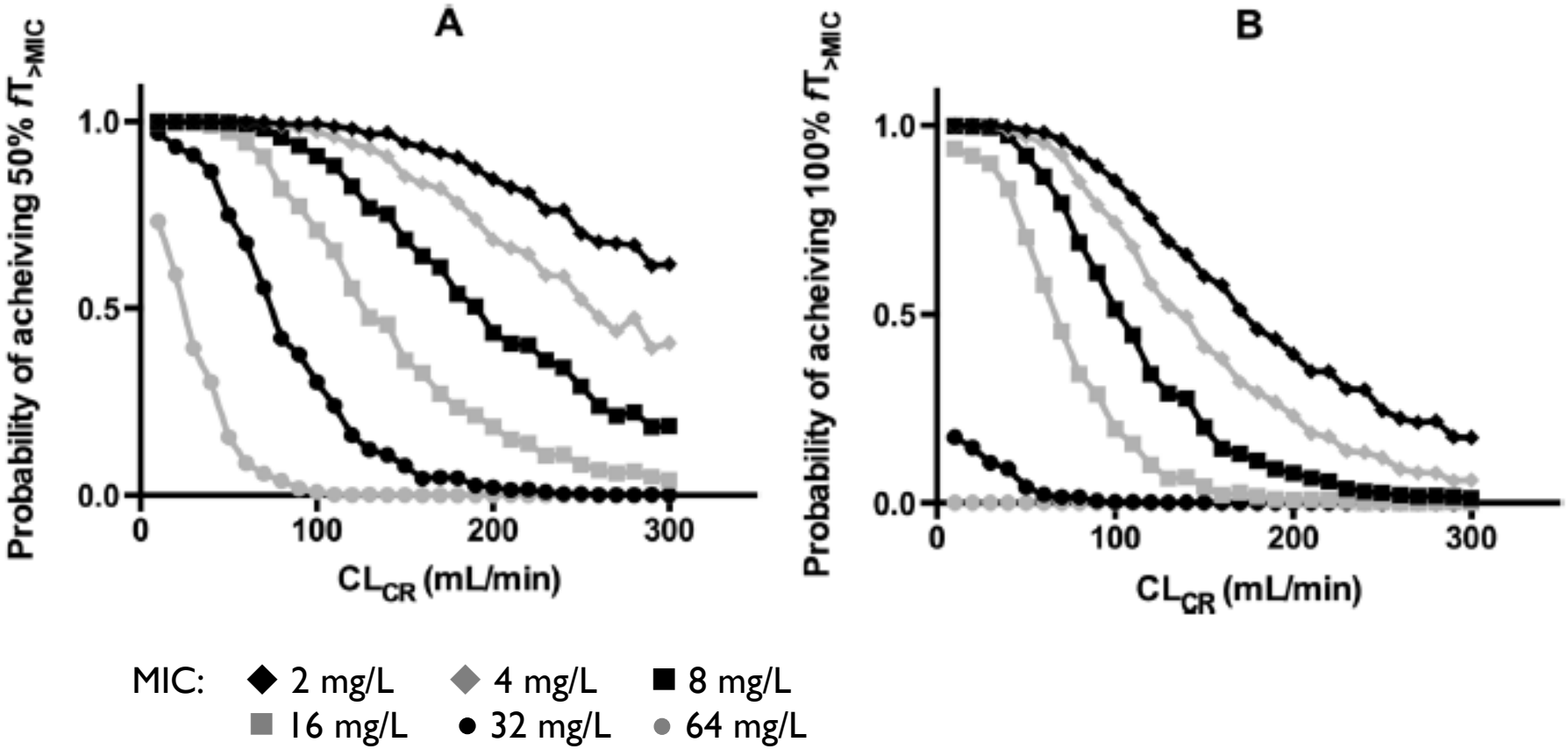
ARC AND PHARMACOKINETIC TARGETS

Piperacillin/tazobactam Dose with ARC

Design	• Single-center • Observational
Population	• n = 48 • Ages18 - 80 • Sepsis
Intervention	• Piperacillin/tazobactam 4.5 grams every 6 hours over 20 minutes • Antibiotic plasma concentrations at several time points; C_{min}= 360 minutes post infusion • 24-hour urine collection

Udy, et al. *Critical Care* 2015(19):28

Probability of Target Attainment



Udy, et al. *Critical Care* 2015(19):28

Vancomycin Optimization with ARC

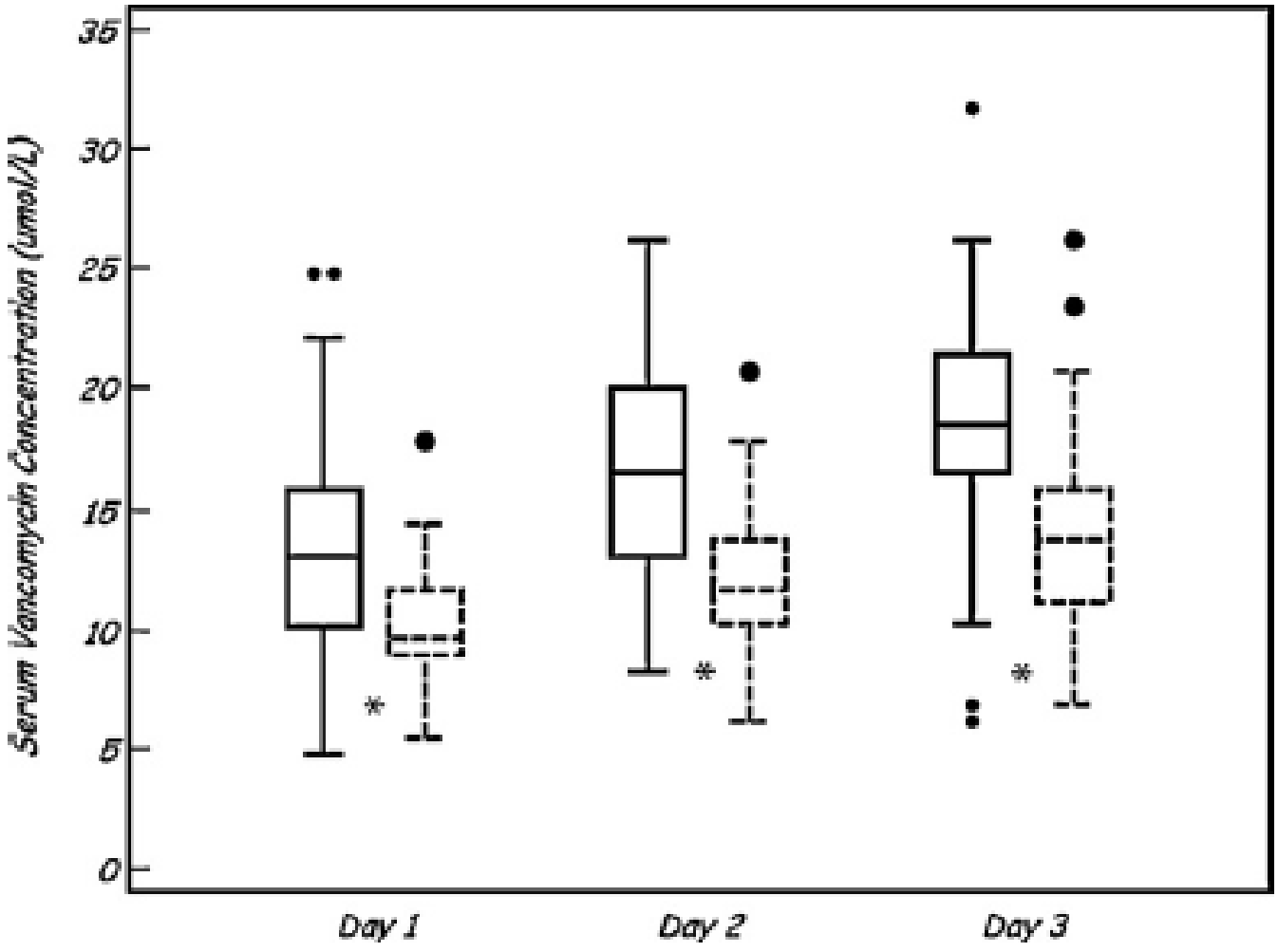
Design	• Prospective • Single-center • Observational cohort study
Population	• n = 93 • Severe sepsis or septic shock • Ages 18 - 80 • Ventilated
Intervention	• Vancomycin loading dose followed by 30 mg/kg/day infusion over 24 hours • Daily analysis of serum vancomycin levels (Days 1 to 3) • 24-hour urine collection • Compare CrCL ≤ 130 mL/min and CrCL > 130 mL/min

Baptista, et al. *Int Journ of Antimicrobial Agents* 2012;39:420-3

Median Serum Vancomycin Concentrations

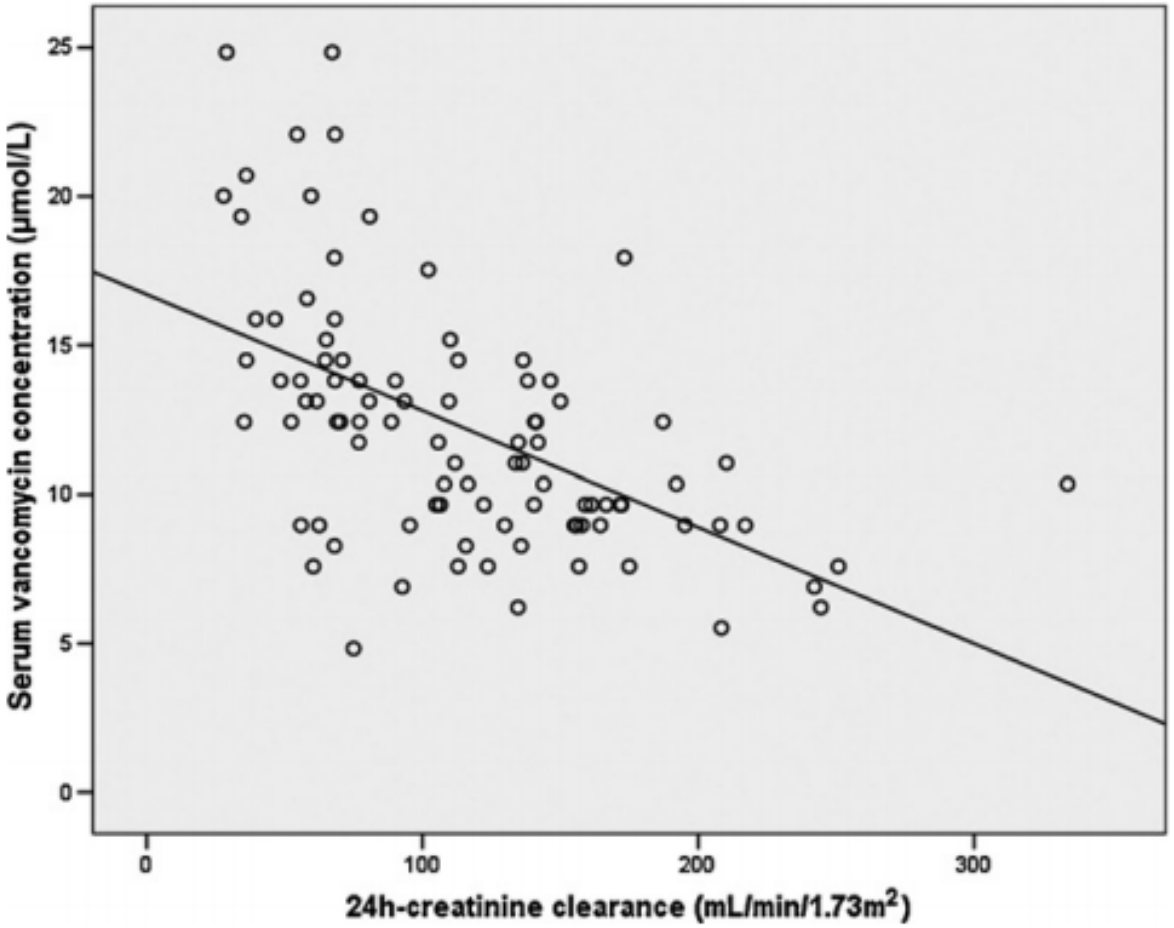
Group A (solid):
CrCL ≤ 130 mL/min

Group B (dotted):
CrCL > 130 mL/min



Baptista, et al. *Int Journ of Antimicrobial Agents* 2012;39:420-3

Vancomycin Concentration and CrCL



Take Away:

- Direct correlation of vancomycin concentration and CrCl
- Day 1 of therapy: 90% of the ARC group subtherapeutic*
- More aggressive dose strategy

*Following a load and infusion started on Day 0

Baptista, et al. *Int Journ of Antimicrobial Agents* 2012;39:420-3

ARC AND CLINICAL OUTCOMES

Mortality in Enterobacteriaceae Bloodstream Infections

Design	• Retrospective cohort study
Population	• n = 494 • Sepsis, severe sepsis or septic shock with positive blood culture of any Enterobacteriaceae organism • Age ≥ 18 years old
Intervention	• Determine whether ARC was prevalent and if it impacts mortality • Calculated CrCL: MDRD and CKD-EPI • ARC defined as CrCL > 130 mL/min/1.73m^2

Burnham et al. *PLoS ONE* 2017;12(7)

ARC and Clinical Outcomes

- Only 5% had ARC
- Multivariate logistic regression analysis, ARC did not influence 30-day mortality

	GFR* ≤ 130 mL/min/1.73m^2 n = 467	GFR* > 130 mL/min/1.73m^2 n = 27	p-value
ICU length of stay, mean days (range)	0.8 (0-4.8)	0.9 (0-4.7)	0.913
30-day mortality, n (%)	64 (13.1)	3 (11.1)	1

* By CKD-EPI or MDRD

Burnham et al. *PLoS ONE* 2017;12(7)

Continuous vs. Intermittent Beta Lactam Therapy and Clinical Outcomes

Design	• Sub-study of the BLING-II trial • Randomized • Placebo-controlled • Multicenter (25 ICUs)
Population	• n = 432 • Severe sepsis receiving piperacillin/tazobactam, ticarcilin/clavulanic acid or meropenem by continuous or intermittent infusion
Intervention	• Loading dose and randomized to continuous infusion or intermittent infusion • Measured CrCL • ARC defined as CrCL ≥ 130 mL/min

Udy, et al. *Int Journ of Antimicrobial Agents* 2017;49:624-630

Comparison of Clinical Outcomes

	All Patients n = 254	No ARC CrCL < 130 mL/min n = 209	ARC CrCL ≥ 130 mL/min n = 45	p-value
ICU free days at day 28, median (IQR)	21(11-24)	21 (11-25)	21 (12-24)	0.89
Clinical cure at 14 days post antibiotic, n (%)	148 (58.3)	115 (55.0)	33 (73.3)	0.024
Length of ICU stay, median days (IQR)	6 (3-11)	5 (3-11)	7 (4-12)	0.37
90-day mortality, n (%)	47 (18.5)	41 (19.6)	6 (13.3)	0.33

Udy, et al. *Int Journ of Antimicrobial Agents* 2017;49:624-630

Comparison of Continuous vs. Intermittent Beta Lactam Administration

	ARC CrCL ≥ 30 mL/min n = 45			No ARC CrCL < 130 mL/min n = 209		
	CI n = 19	II n = 26	p-value	CI n = 103	II n = 106	p-value
ICU free days at day 28, median (IQR)	20 (10-24)	23 (16-24)	0.44	20 (11-24)	22 (10-25)	0.40
Clinical cure at 14 days post antibiotic, n (%)	14 (73.7)	19 (73.1)	0.96	60 (58.3)	55 (51.9)	0.36
90-day mortality, n (%)	2 (10.5)	4 (15.4)	0.64	19 (18.4)	22 (20.8)	0.67

CI: Continuous infusion beta lactam II: Intermittent infusion beta lactam therapy

Udy, et al. *Int Journ of Antimicrobial Agents* 2017;49:624-630

Summary

- ARC is not fully understood
- Calculated CrCL does not correlate well with measured CrCL
- Consider measured CrCL and suspect ARC in high risk patients who may not be clinically improving as expected
- The current literature does not suggest ARC affects clinical outcomes

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