Antibiotic Resistance Issues for the Intensivist and Pulmonologist

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Disclosures

I have received consulting fees from:

- Allergan
- Merck
- Pfizer
- Tetraphase
- Shionogi

Objectives

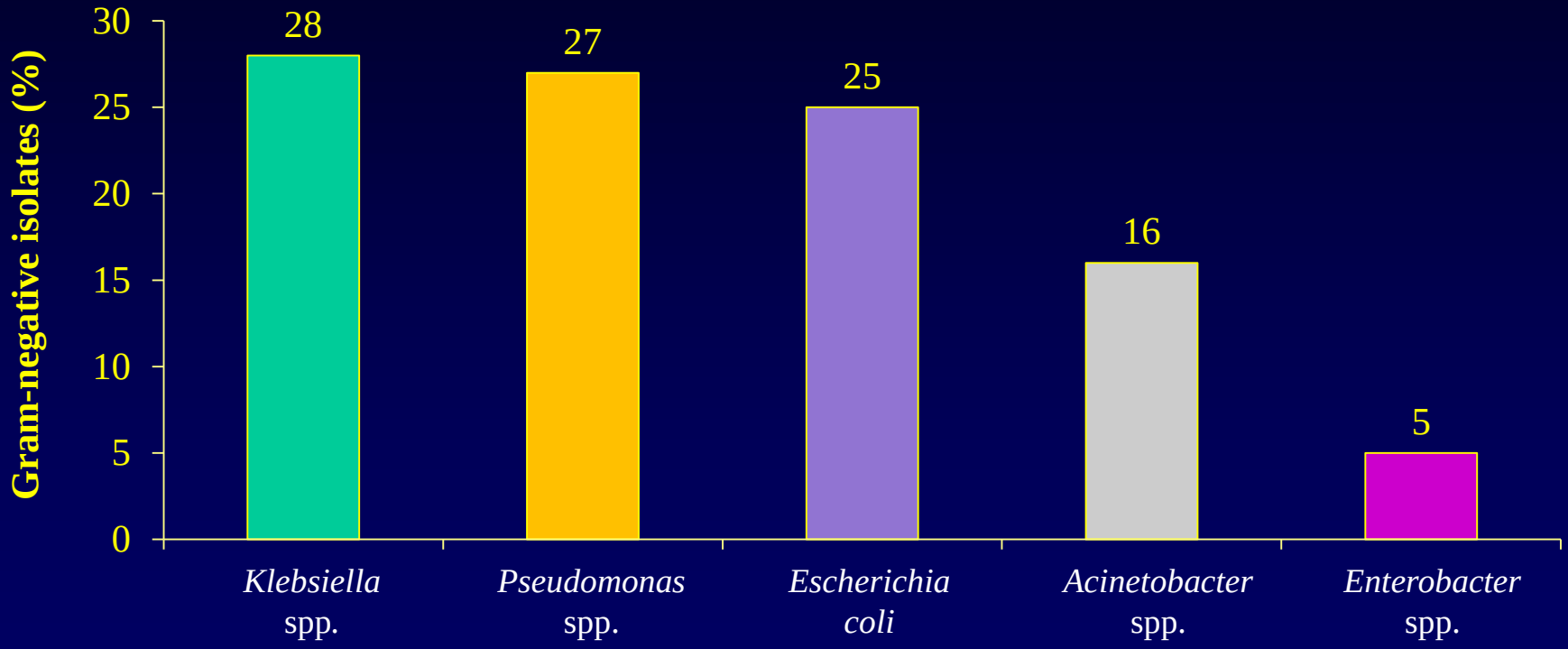
- Upon completion of this activity, participants should be able to
  - Describe the prevalence of antibiotic resistance
  - Appreciate novel issues in antibiotic use in the ICU
  - Understand the importance of recently approved antibiotics

The Dilemma

- Appropriate antibiotics key determinant of outcome in the ICU
- Resistance rates increasing
- Most data for use of antibiotics derive from studies in non-ICU subjects and ignores unique ICU issues (eg fluid resuscitation, MV, changing renal fxn)
- How do we optimize antibiotic administration in the ICU?

Globally, Majority of ICU infections Are Due to Gram-negative Bacteria

37% of GNR infections are MDR*



*50% of *Klebsiella* and 27% of *E. coli* are ESBL or CRE; 16% of *Pseudomonas* and 70% of *Acinetobacter* are Carbapenem resistant

Vincent JL, et al. JAMA 2020; 323: 1478-87.

Impact of Resistance on Outcomes:
How Many Time Do We Have to Get it Right to Save One Life?

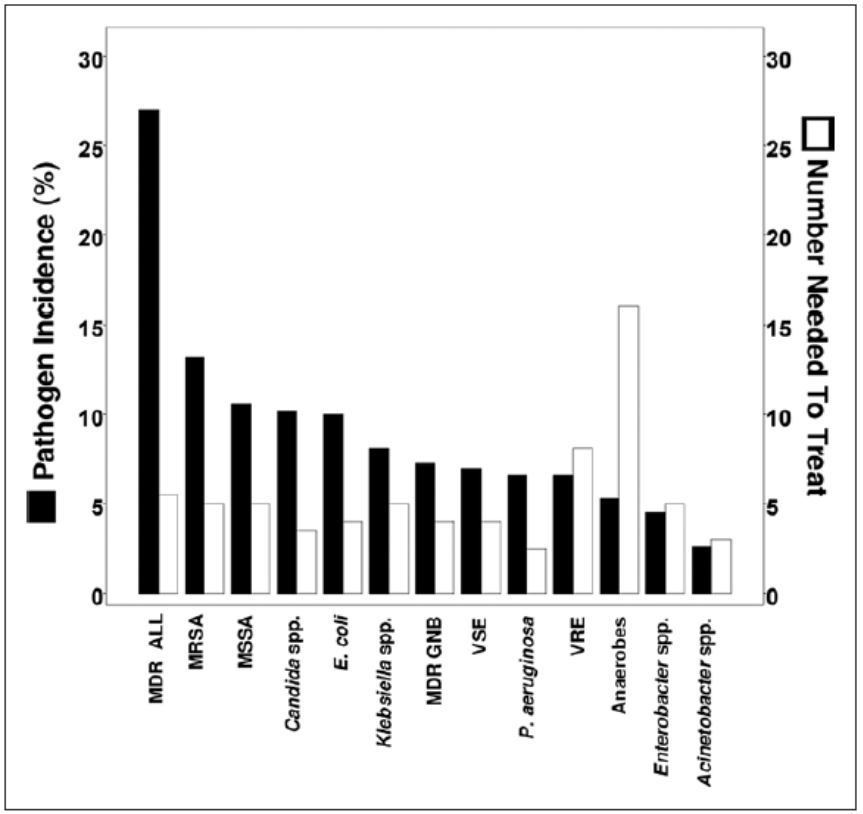


Figure 1. Bar graphs for pathogen prevalence associated with severe sepsis and septic shock (*black bars*) and the number needed to treat with appropriate therapy to prevent one patient death (*white bars*). MDR = multidrug resistance; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; VSE = vancomycin-susceptible enterococci; VRE = vancomycin-resistant enterococci.

- Retrospective analysis of impact of appropriate therapy on mortality
- 1250 subjects with septic shock
- Inappropriate antibiotics: 3.4 x independent increase in risk for death
- NNT calculated per pathogen

For every 5 patients given appropriate therapy one added survivor!

Vazquez-Guillamet C, et al. CCM 2014; 42: 2342-9.

Outcomes: Predictors in GNR Septic Shock

Table 3 Predictors of hospital mortality[a]

	Odds ratio	95% confidence interval	*P* value
Non-IAAT	3.872	2.770 to 5.413	<0.001
Chronic liver disease	1.942	1.319 to 2.860	0.001
Septic shock	1.846	1.335 to 2.553	<0.001
Pneumonia	1.766	1.237 to 2.522	0.002
Mechanical ventilation	1.669	1.172 to 2.376	0.005
APACHE II score (per 1 point)	1.076	1.047 to 1.105	<0.001
Surgery	0.701	0.560 to 0.879	0.002
Admitted from home	0.677	0.489 to 0.936	0.018
Urosepsis	0.675	0.469 to 0.972	0.034

- Retrospective analysis
- Subjects: GNR bacteremia resulting in septic shock
- N=1064
  - E. coli: 27%
  - K. pneumoniae : 20%
  - P. auerginosa: 17%
- Endpoint: Mortality

Zilberberg MD, et al. Crit Care Med 2014. 18: 596.

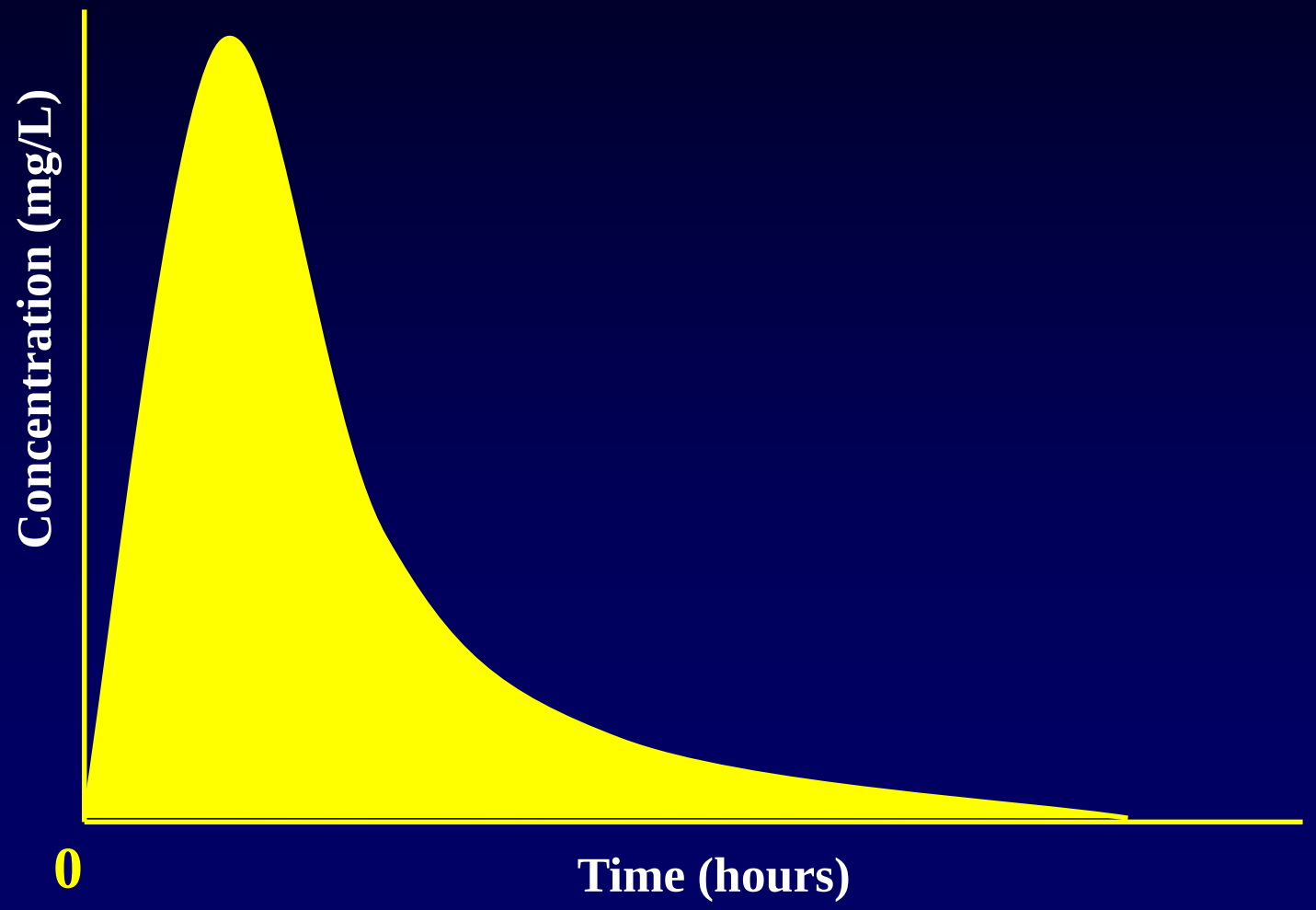
Inappropriate Therapy: A Modifiable Risk Factor

Table 4 Predictors of receiving initially inappropriate antibiotic therapy[a]

	Odds ratio	95% confidence interval	*P* value
Multidrug resistant	13.05	7.00-24.31	<0.001
HIV	3.64	1.02-12.95	0.046
Transferred from another hospital	2.86	2.00-4.08	<0.001
Nursing home resident	2.28	1.35-3.84	0.002
Prior antibiotics	2.06	1.47-2.87	<0.001
Polymicrobial	1.90	1.30-2.77	0.001
Congestive heart failure	1.61	1.11-2.35	0.013
APACHE II score (per 1 point)	1.05	1.02-1.07	<0.001

PK/ PD: Part of the Solution

Serum antibiotic levels over a dosing interval



PK
(Pharmacokinetics)

- **Pharmacokinetics** describes the **concentration-time** profile of a drug (in this case antibiotic) in the body

PD
(Pharmacodynamics)

- **Pharmacodynamics** correlates the **concentration** of the antibiotic with its **ability to kill** or inhibit the target pathogen

PK-PD Relationship

PK Dose → concentration

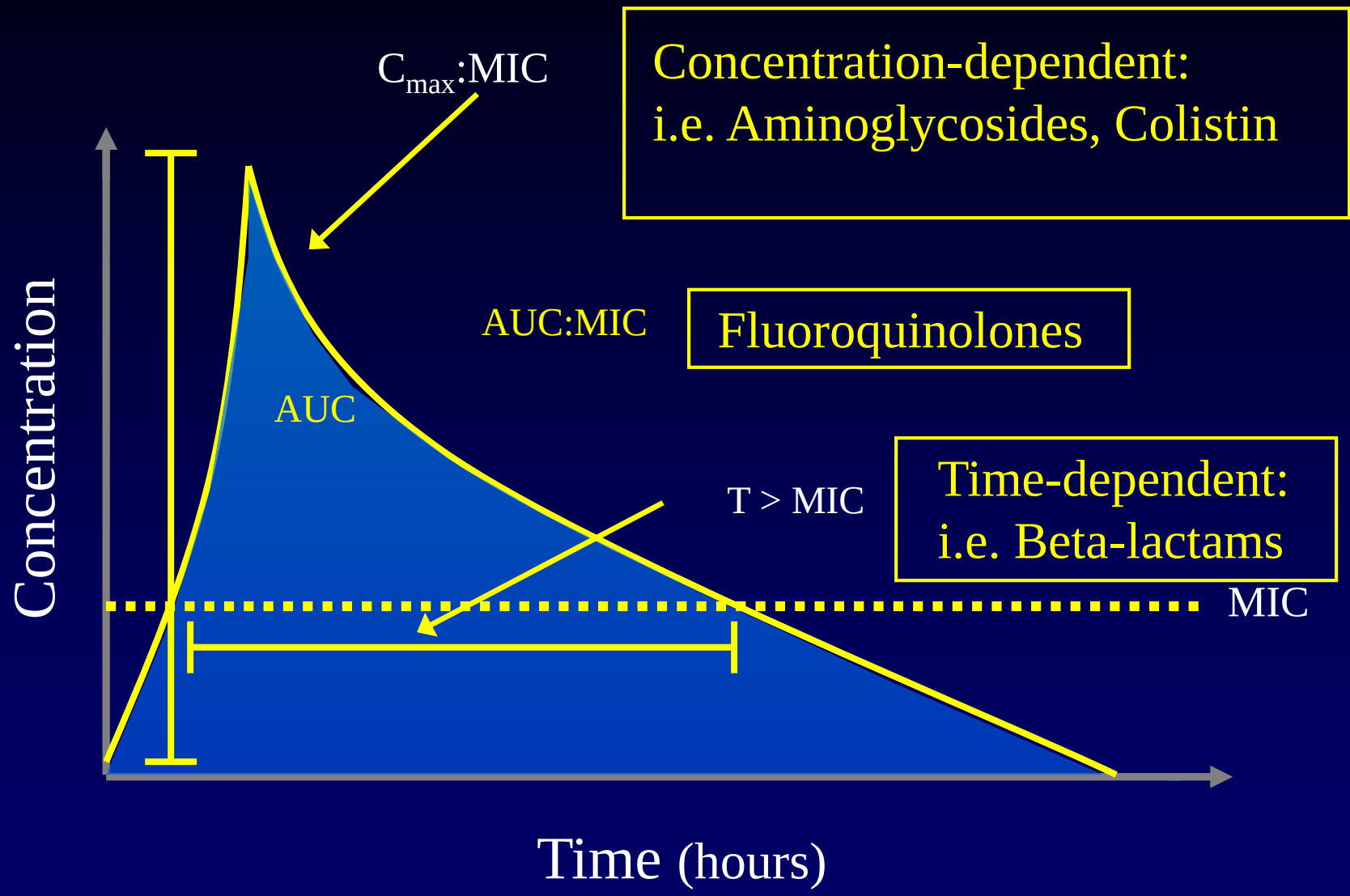
PD Concentration → effect

PK-PD Dose → concentration → effect

Dose —PK→ concentration —PD→ effect

PK-PD Relationship

Antimicrobial Pharmacodynamics



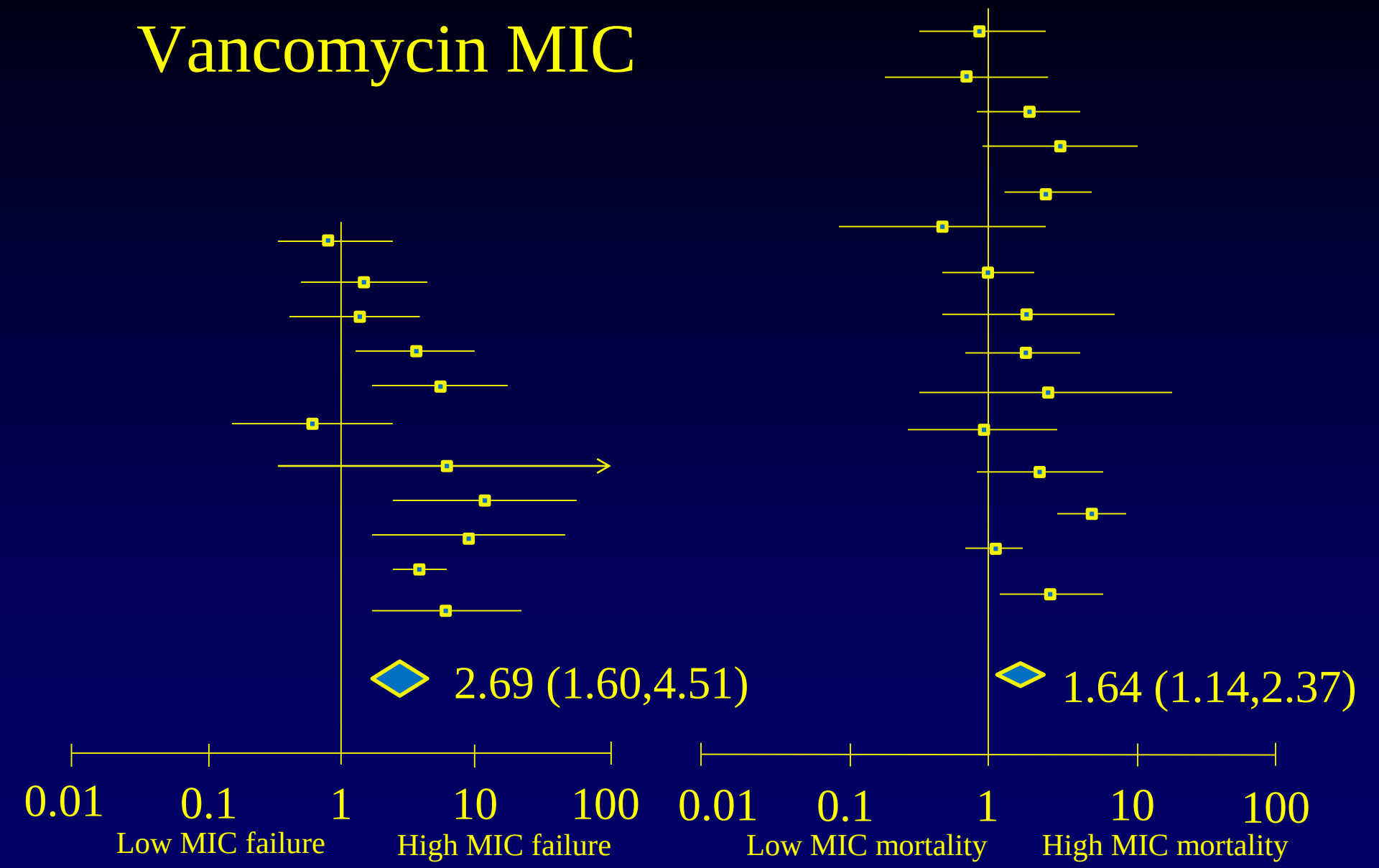
Increased Vancomycin Use Not Improving Rates of Bactericidal Activity in Pneumonia

	AUC/MIC ratio ≥400		
MIC value	**0.5mg/L (%)**	**1.0mg/L (%)**	**2.0mg/L (%)**
500 mg IV Q12H	**57**	**15**	**0.7**
1000 mg IV Q12H	**90**	**57**	**1.5**
1500 mg IV Q12H	**97**	**79**	**38**
2000 mg IV Q12H	**98**	**90**	**57**

MIC = minimum inhibitory concentration
AUC = area under the curve (exposure)

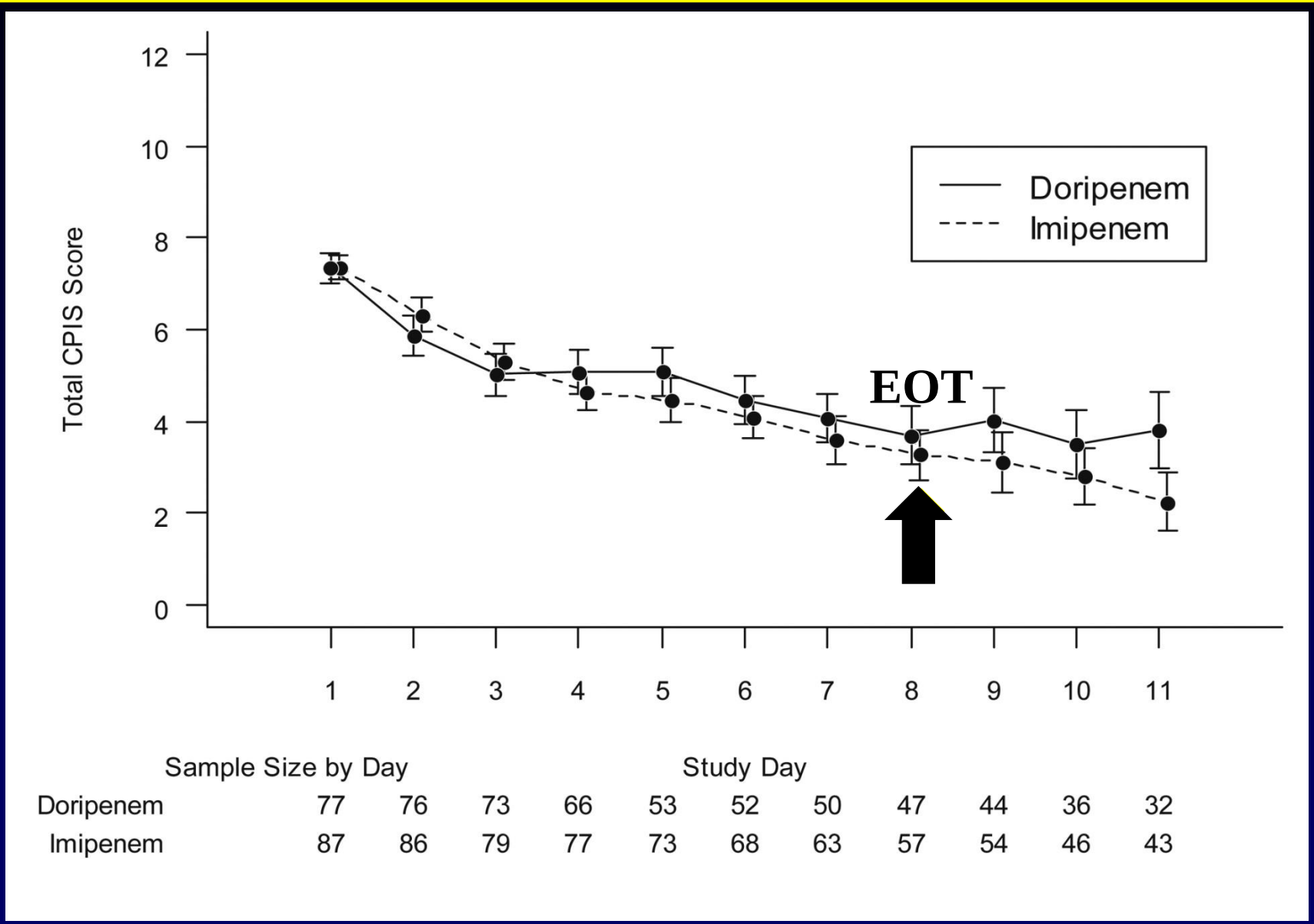
Patel et al. CID. 2011;52(8):969-974

Clinical Outcome: Vancomycin MIC



Van Hal SJ et al. Clin Infect Dis 2012;54:755-71

CPIS for *Pseudomonas aeruginosa* MITT

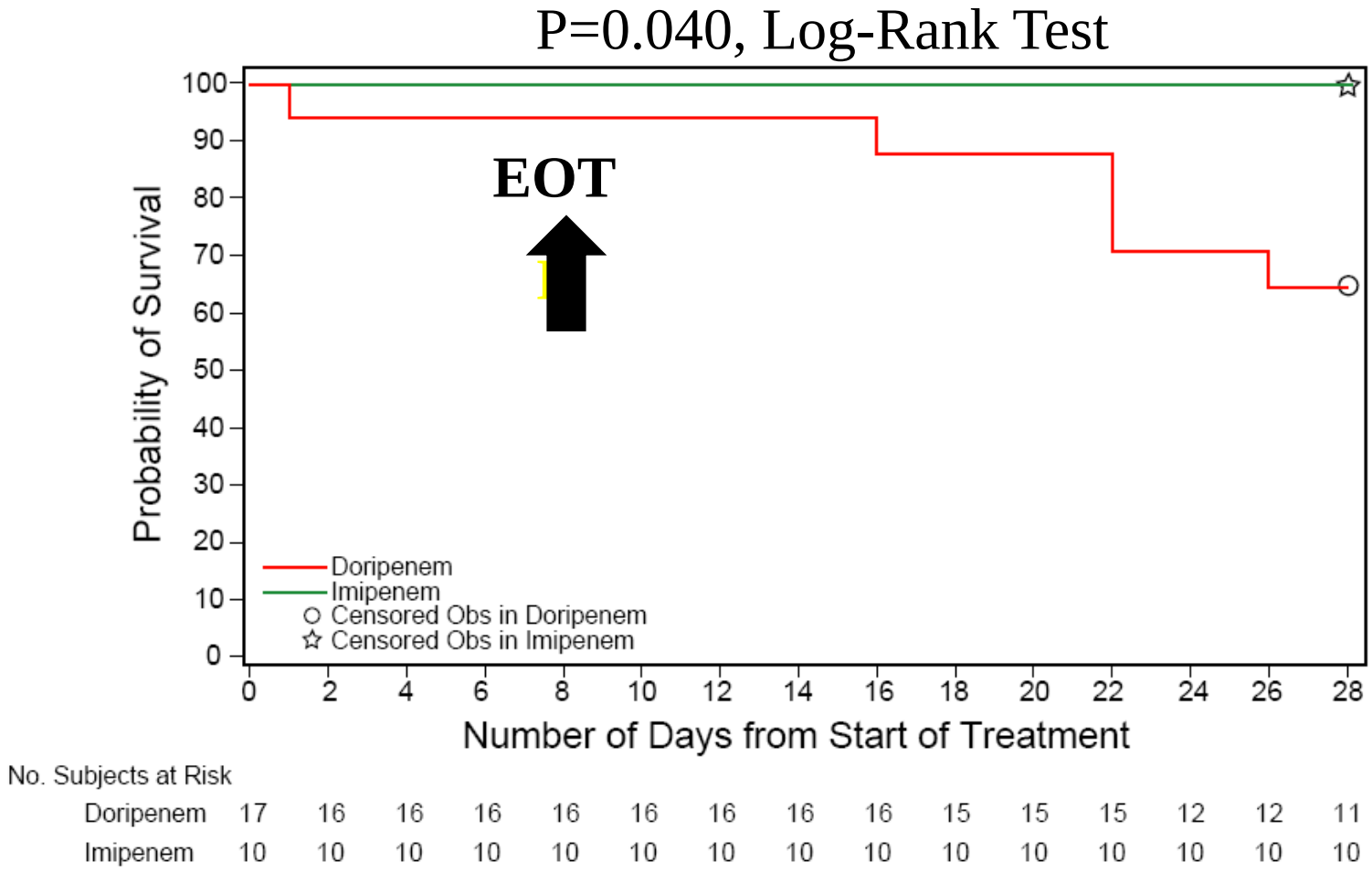


Sample Size by Day											
Doripenem	77	76	73	66	53	52	50	47	44	36	32
Imipenem	87	86	79	77	73	68	63	57	54	46	43

Kollef, MH, et al. Crit Care 2012;16(6):R218.

Washington University in St. Louis

28-Day All Cause Mortality: *P. aeruginosa*



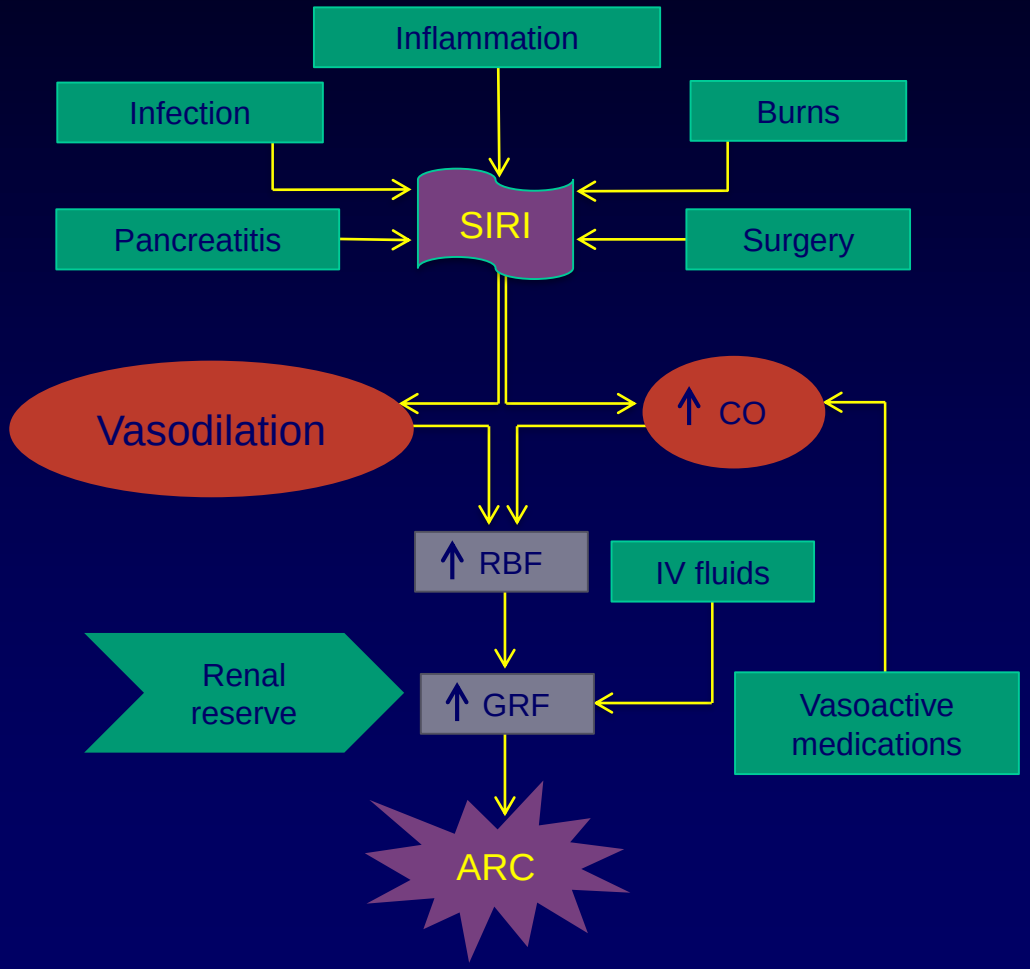
Kollef, MH, et al. Crit Care 2012;16(6):R218.

Washington University in St. Louis

Renal Function

- Most agents cleared by the kidneys and common place to dose reduce based on estimated GFR
- However
  - Estimated GFR poor correlate of true CrCl
  - CrCl changes over time in critically ill
- What about if CrCl elevated?

Explanation of Augmented Renal Clearance

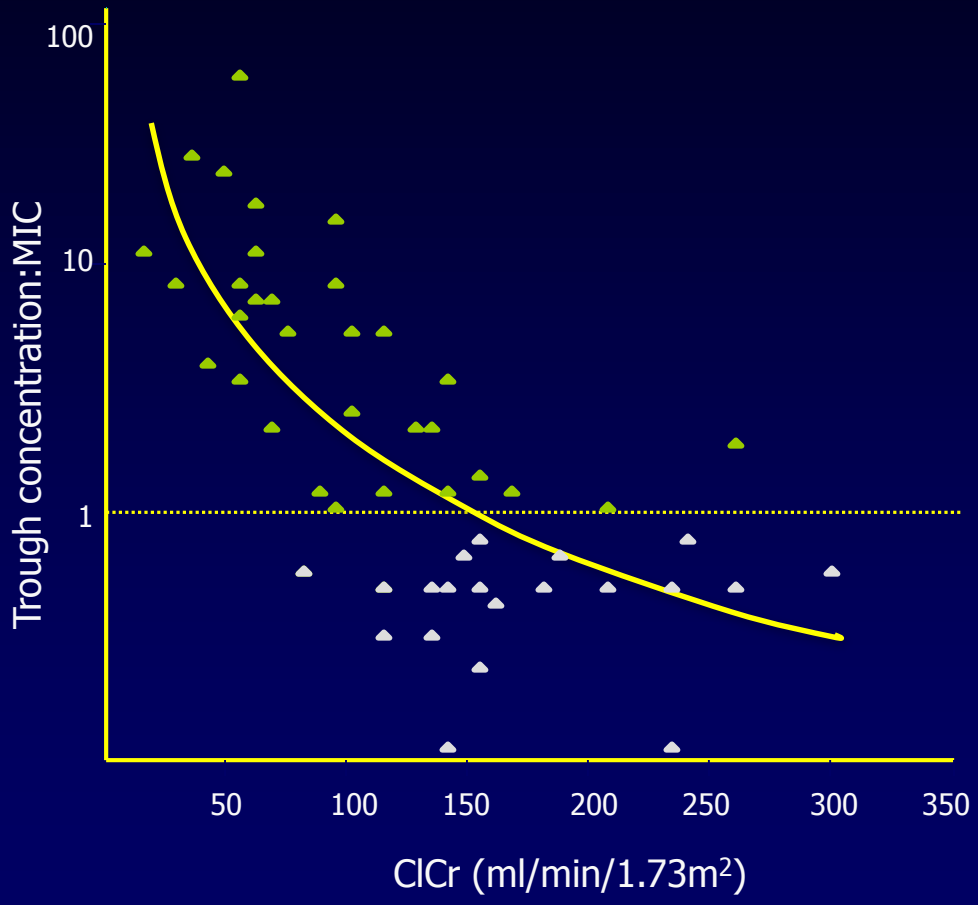


- ARC arises from interaction of:
  - Systemic inflammation
  - Physiologic reserve
- ARC noted in:
  - Young patients
  - Trauma patients

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

β-lactam Underdosing in Patients with Augmented Renal Clearance (ARC)?

- ARC = supranormal glomerular filtration
- ClCr > 130 ml/min/1.73m^2
- Cockcroft Gault CrCl
- Most common in critically ill patients with:
  - SIRS/Sepsis
  - Trauma



Baptista JP et al. Crit Care 2011;15:R139.

Udy AA et al. Chest 2012;142:30-39.

Dosing Matters: Was This All Due to ARC?

Infection type	Treatment group	Predicted mortality* (%)	Actual mortality (%)
Non-VAP	Ceftobiprole	18.5	18.8
Non-VAP	Linezolid/Ceftazidime	19.0	21.2
VAP	Ceftobiprole	24.2	33.7
VAP	Linezolid/Ceftazidime	24.2	22.6

Ceftobiprole 500 mg q 8 vs Linezolid 600 mg q 12 hours & Ceftazidime 2 g q 8

*Based on Knaus et al. Crit Care Med 1985;13:818

Study primary enrolled

-Young patients with normal estimated renal function

-Trauma patients

Basilea (On File)

Clinical Cure & All-Cause 28-Day Mortality

	Doripenem 7-day course			Imipenem 10- day course				
	n	N	%	n	N	%	Diff (%)	95% CI
Clinical cure rate								
MITT	36	79	**45.6**	50	88	**56.8**	-11.2	**(-26.3; 3.8)**
ME	28	57	**49.1**	36	59	**66.1**	-17.0	**(-34.7; 0.8)**
Creatinine clearance* (MITT)								
≥ 150 mL/min	**8**	**18**	**44.4**	**20**	**28**	**71.4**	**-27.0**	**(-55.4; 1.4)**
≥80 - 150	31	15	48.4	37	19	51.4	-3.0	-26.8; 20.9
>50 - <80	23	12	52.2	18	9	50.0	2.2	-28.7; 33.0
>30 - ≤50	5	0	0	2	1	50.0	-50.0	
≤30	2	1	50.0	3	1	33.3	16.7	
All cause 28-day mortality								
MITT	17	79	21.5	13	88	14.8	6.7	(-5.0; 18.5)

MITT = Microbiological ITT, ME = Microbiologically Evaluable

* Calculated using Cockcroft -Gault formulas relating serum creatinine with age & body weight

Kollef, MH, et al. Crit Care 2012;16(6):R218.

Novel Dosing Approaches in the ICU: Extended Infusion

- DBRCT
- Continuous infusion beta-lactam vs intermittent bolus
- Subjects: severe sepsis (n=60)
- Primary Endpoint:
  - Plasma drug conc above pathogen MIC on days 3 and 4
- Secondary endpoint:
  - Clinical response

Endpoint	Intervention Group	Control Group	*P*
Plasma antibiotic concentration >MIC	18 (81.8%)[a]	6 (28.6%)[a]	.001
Clinical cure (test of cure date)	23 (76.7%)	15 (50.0%)	.032
Clinical cure (test of cure date with treatment exclusions)	21 (70.0%)	13 (43.3%)	.037
Clinical cure (last day of blinding)	9 (30.0%)	6 (20.0%)	.37
Time to clinical resolution (days)	11 (6.75–24.25)[b]	16.5 (7–28)[b]	.14
Time to resolution of CRP (days)	6 (2.5–22.5)[c]	5 (3–27)[c]	.79
ICU length of stay (postrandomization)	7.5 (4–12)	9 (5–14.25)	.50
ICU-free days			
All	19.5 (12.75–24)	17 (.75–22)	.14
ICU survivors	20.5 (16–24)[d]	18 (12.75–22)[d]	.22
ICU survival	28 (93.3%)	26 (86.7%)	.67
Hospital survival	27 (90.0%)	24 (80.0%)	.47

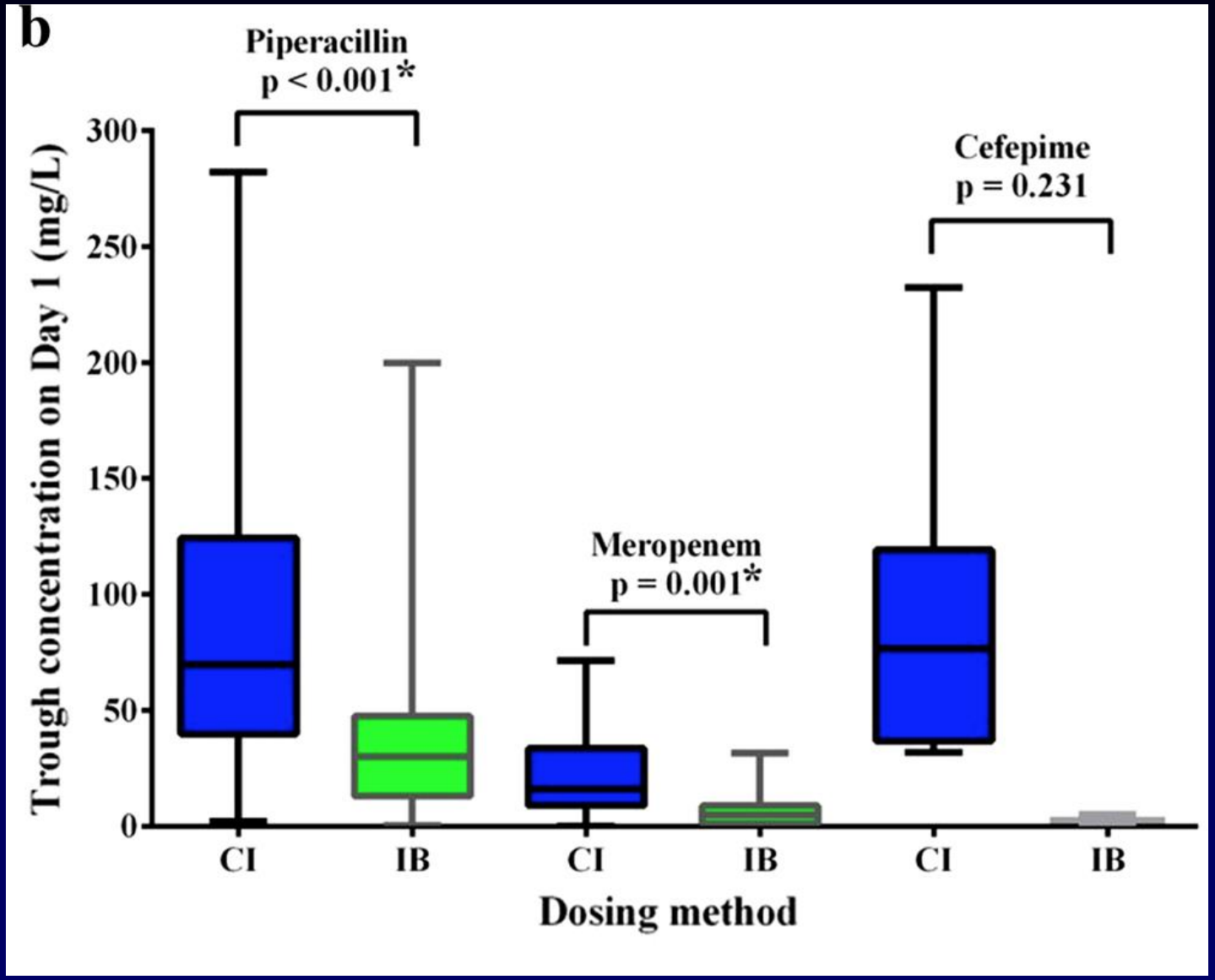
Dulhunty JM, et al. Clin Infect Dis 2013; 56: 236-44

Beta-Lactam (BL) Infusion in Severe Sepsis Trial

- Prospective, randomized, non-blinded
- Interventions
  - Bolus infusion (BI) of BL vs
  - Continuous infusion (CI)
- Agents: cefipeme, pip/taz, meropenem
- Subjects: (n=140), Adults, severe sepsis, & organ dysfunction
- Endpoints
  - Clinical cure 14d after d/c abx
  - PK/PD targets (BL levels measured in central lab)

Abdul Aziz MH, et al. ICM; published online Jan. 2016

BLISS



Abdul Aziz MH, et al. ICM, 2016: 42: 1535-45.

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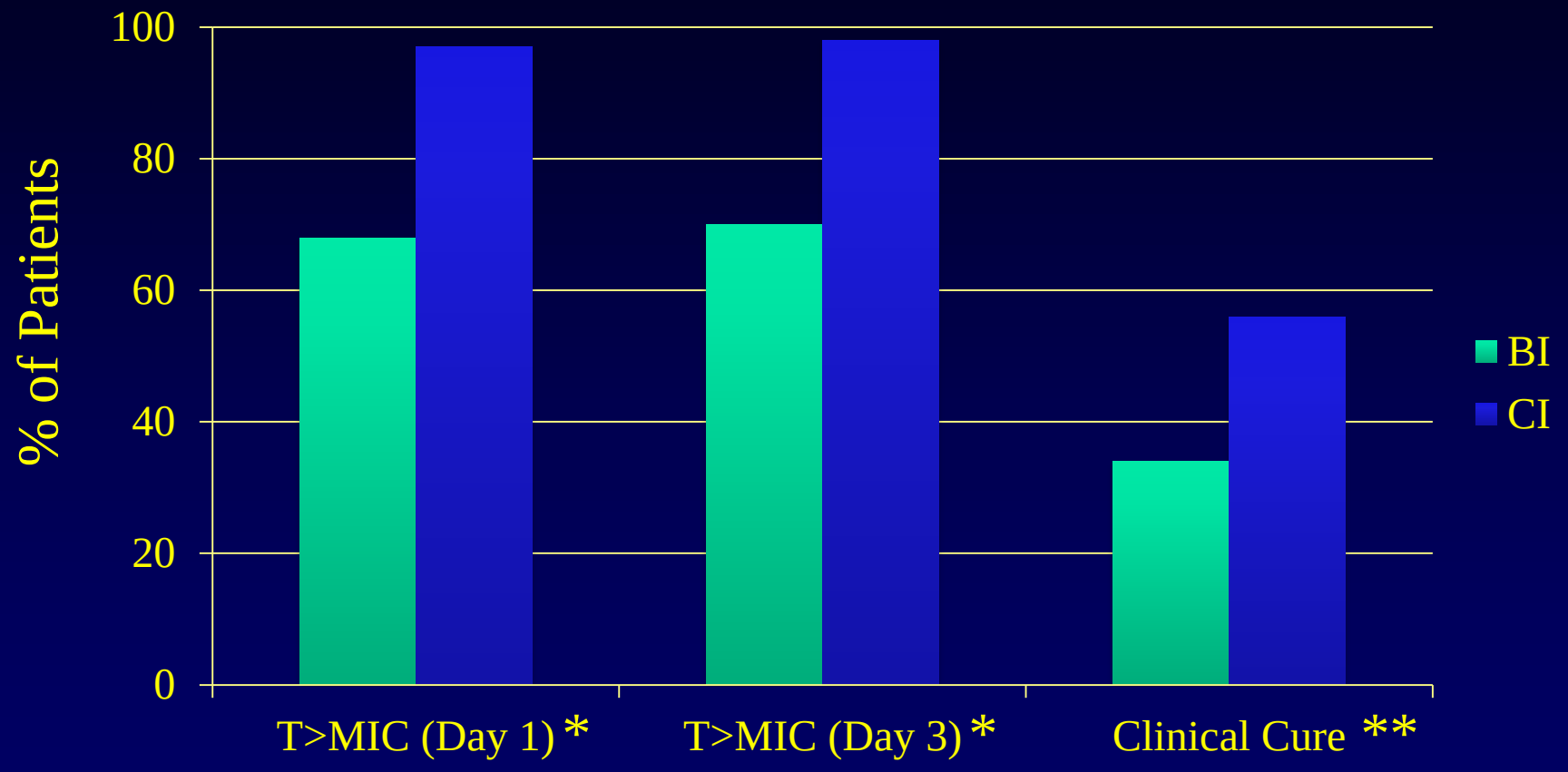
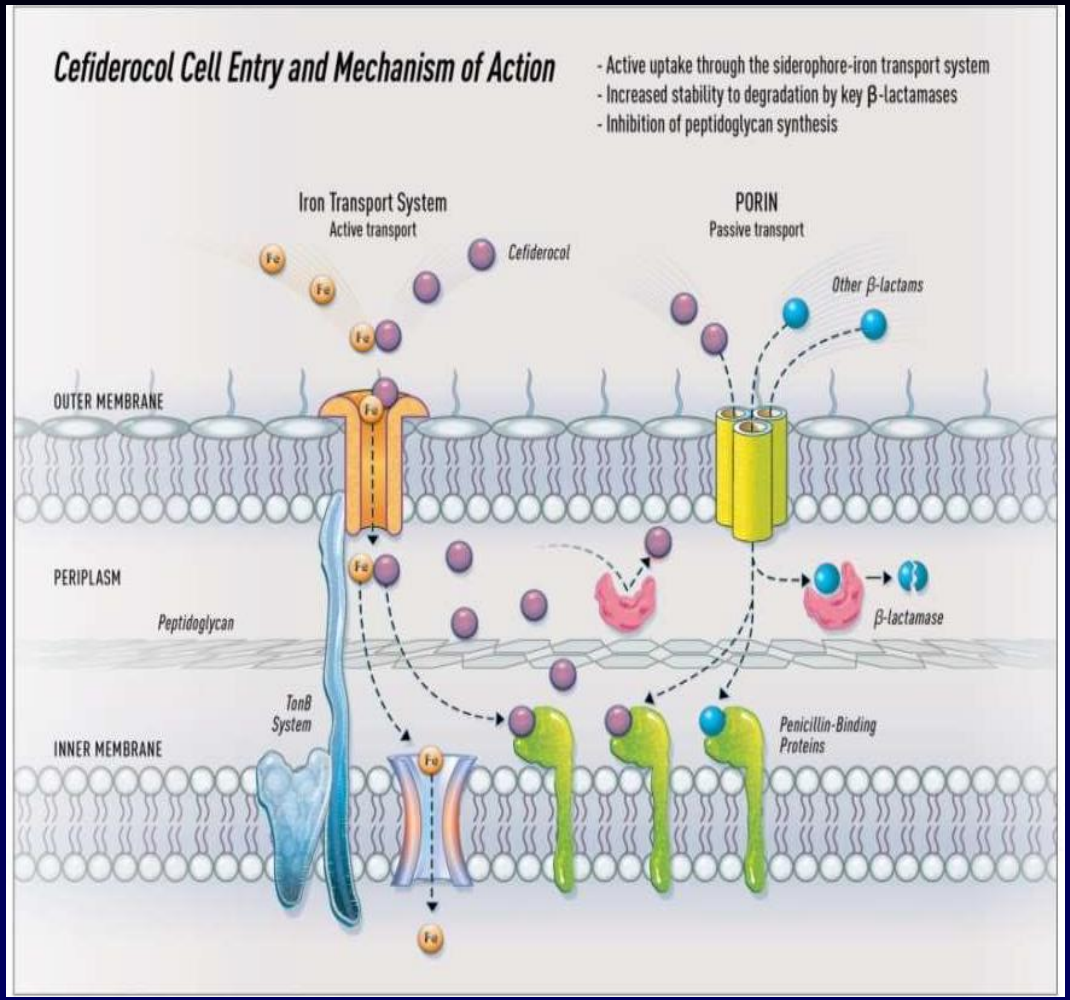


*p<0.001, **p<0.01

Abdul Aziz MH, et al. ICM, 2016: 42: 1535-45.

Cefiderocol

- Siderophore cephalosporin with a catechol moiety and binds mainly to PBP-3
- Forms a chelating complex with ferric iron
- Superior *in vitro* activity vs β-lactam comparators against ESBL-, KPC- or metallo-β-lactamase-positive Enterobacteriaceae isolates, and both MDR *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* strains
- Completed trial in cUTI



High stability to B-lactamases and rapid, active uptake through the iron transport system (almost not affected by classic efflux pump systems).

27th ECCMID, Vienna, Austria 2017; abstract OS0250D; IDWeek, San Diego, CA 2017; abstract 1869

Falagas ME, et al. *Expert Rev Anti Infect Ther* 2016; 14:747-763.

Cefiderocol

Pneumonia Trial

- -1:1 randomization: cefiderocol 2 g q8h vs meropenem 2 g q8h
- -Non-inferiority design
- -Included both VAP and HAP
- -n=298; *K. pneumoniae* most common pathogen (40%)

Outcome	Cefiderocol	Meropenem	p
14 d Mortality	12.4%	11.6%	NS
28 d Mortality	21.0%	20.5%	NS
Clinical cure	64.8%	66.7%	NS

Wunderink RG, et al. OFID 2019; 6: s994.

CREDIBLE-CR

- Open label, RCT
  - Carbapenem resistant pathogens
- Cefidericol vs Best Available Therapy (BAT)
  - BAT mainly colistin based
- Multiple infectious syndromes included (pneumonia, sepsis, UTI, etc)
- n=152 (2:1 randomization)

- Approx 35% of isolates *A. bumanni*
- Clinical cure rates:

Cefidericol (52.5%);

All-Cause Mortality at Day 14, Day 28, and Day 49 in the CREDIBLE-CR Trial

Timepoint	Cefiderocol (n = 101)	BAT (n = 49)	Difference	95% CI
Day 14	19/101 (18.8)	6/49 (12.2)	6.6	-5.4 to 18.5
Day 28	25/101 (24.8)	9/49 (18.4)	6.4	-7.3 to 20.1
Day 49	34/101 (33.7)	10/49 (20.4)	13.3	-1.3 to 27.8

Unadjusted Hazard Ratio for death at Day 49: 1.77; 95% CI: 0.87-3.57. p=0.11

FDA briefing document available at: www.fda.gov/media/131703/download

Ceftolozane - Tazobactam

- Advanced generation cephalosporin
- Cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa* and ESBL-producing strains
- FDA approval in December 2014, EMA 2015
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intra-abdominal Infections (plus metronidazole)
  - IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)
- Plasma-to-epithelial lining fluid penetration ~50%
- Pneumonia at an increased dose: 3.0 g (2 g ceftolozane; 1 g tazobactam) q8h as studied in recent clinical trial

Liscio JL, et al. Int J Antimicrob Agents 2015 Jun 14 (Epub)
Chandorkar G, et al. J Antimicrob Chemother 2012; 67: 2463-2469
Nicolau D, et al. J Clin Pharmacol 2015 (Epub); clinicaltrials.gov

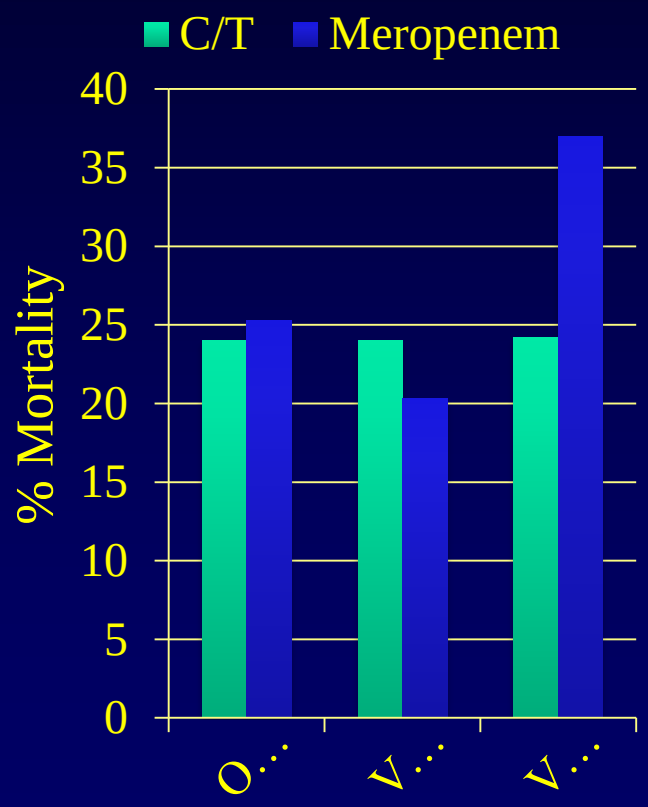
ASPECT-NP

- DBRCT, non-inferiority trial
- Ventilated nosocomial pneumonia
  - Ventilator-associated bacterial pneumonia (VABP)
  - Ventilated hospital-acquired bacterial pneumonia (HABP)
- Interventions
  - Meropenem 1gm q8
  - C/T 3 gm q8
- All patients underwent lower airway sampling
- Stratified by
  - Age (≥65 or <65)
  - VABP vs HABP
- N=726

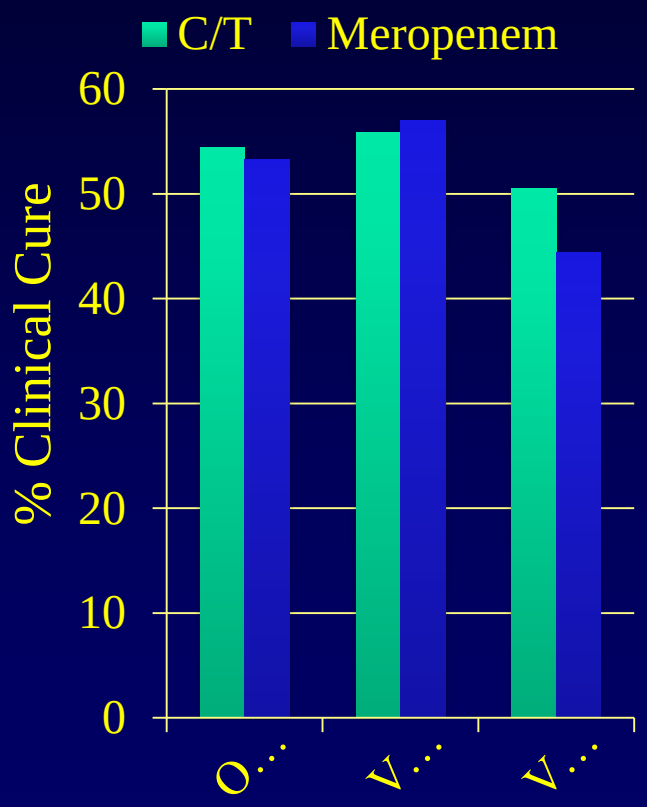
Kollef MH, et al. ECCMID 2019.

ASPECT-NP (Clinical Outcomes)

28-Day All-Cause Mortality (ITT)



Clinical Cure at TOC (ITT)



Kollef MH, et al. ECCMID 2019. #P1917

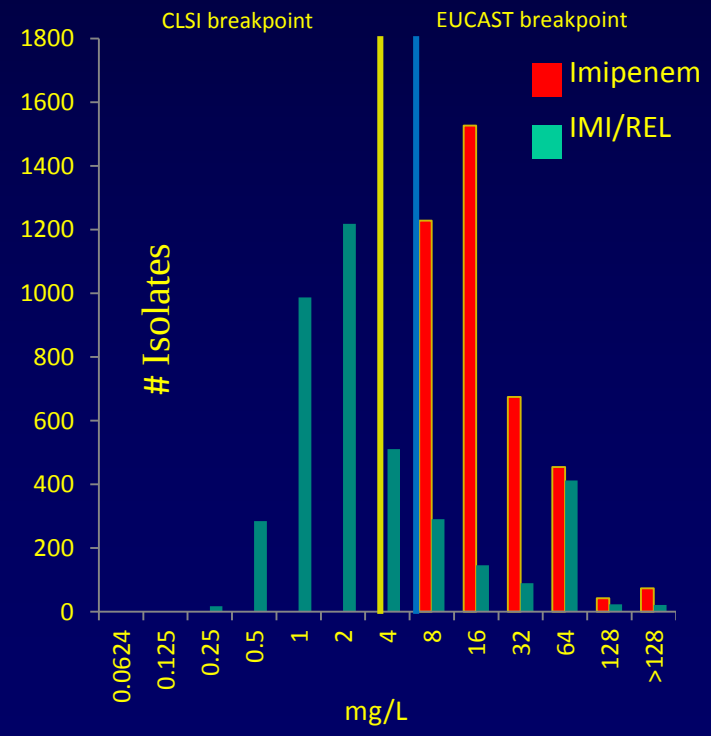
Imi-Rel

- Fixed-dose combination of a β-lactam antibiotic, imipenem (IMI), with a β-lactamase inhibitor, relebactam (REL)
- REL is an inhibitor of Class A and C β-lactamases and restores activity to IMI in resistant Gram-negative bacteria
  - Active in vitro against enterics producing *Klebsiella pneumoniae* carbapenemases (KPC, Class A) and extended-spectrum β-lactamases (ESBL)
  - Active in vitro against Amp-C-producing *Pseudomonas aeruginosa* (Class C)
  - Activity confirmed in in vitro and in vivo animal models

IMIPENEM/RELEBACTAM:
In Vitro Activity – *P. aeruginosa*

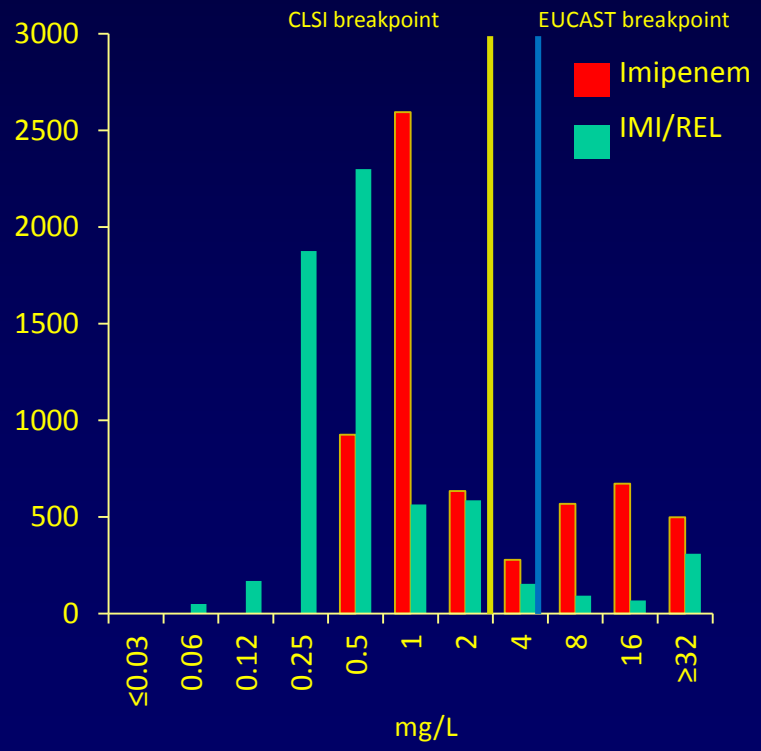
Effect of REL on IMI Susceptibility of IMI-NS *P aeruginosa*

Increased susceptibility to IMI from 0% in the absence of REL to 75% in presence of 4 mg/L REL
N=4002 IMI-NS *P aeruginosa* from challenge panels and surveillance studies



Effect of REL on IMI Susceptibility of Surveillance *P aeruginosa*

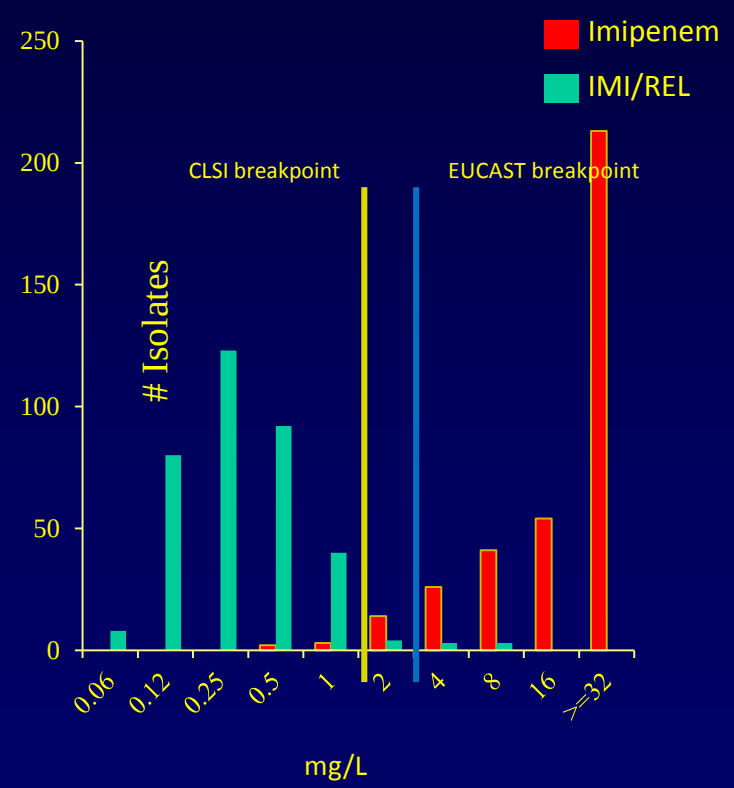
Increased susceptibility to IMI from 73% in the absence of REL to 93% in presence of 4 mg/L REL
N= 6165 SMART Surveillance Isolates 2016



IMIPENEM/RELEBACTAM: In Vitro Activity – Enterobacteriaceae

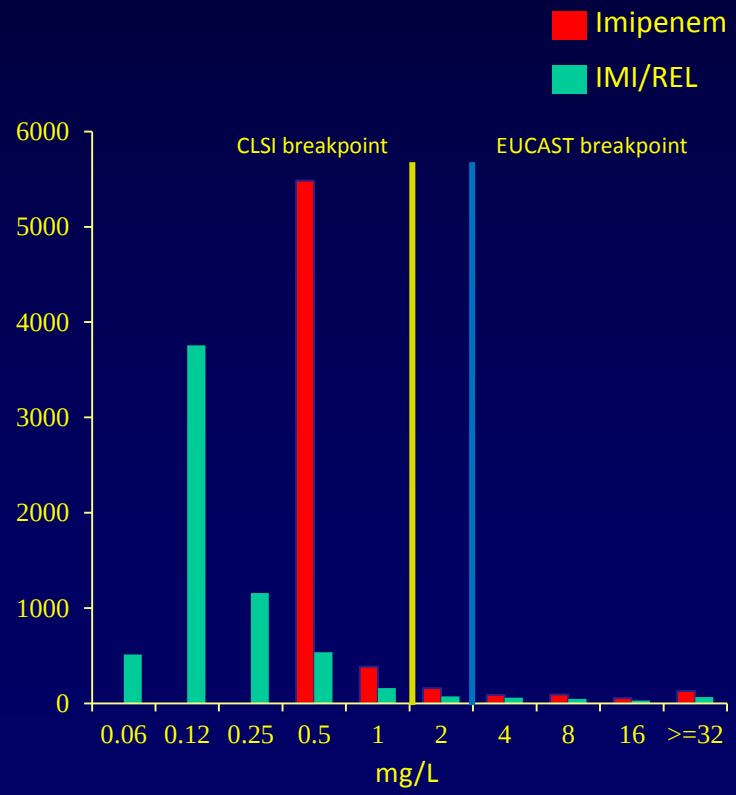
Effect of REL on IMI Susceptibility of KPC-Expressing Enterobacteriaceae

Increased susceptibility to IMI from 5% in the absence of REL to 98% in presence of 4 mg/L REL
N=353 from SMART surveillance 2016

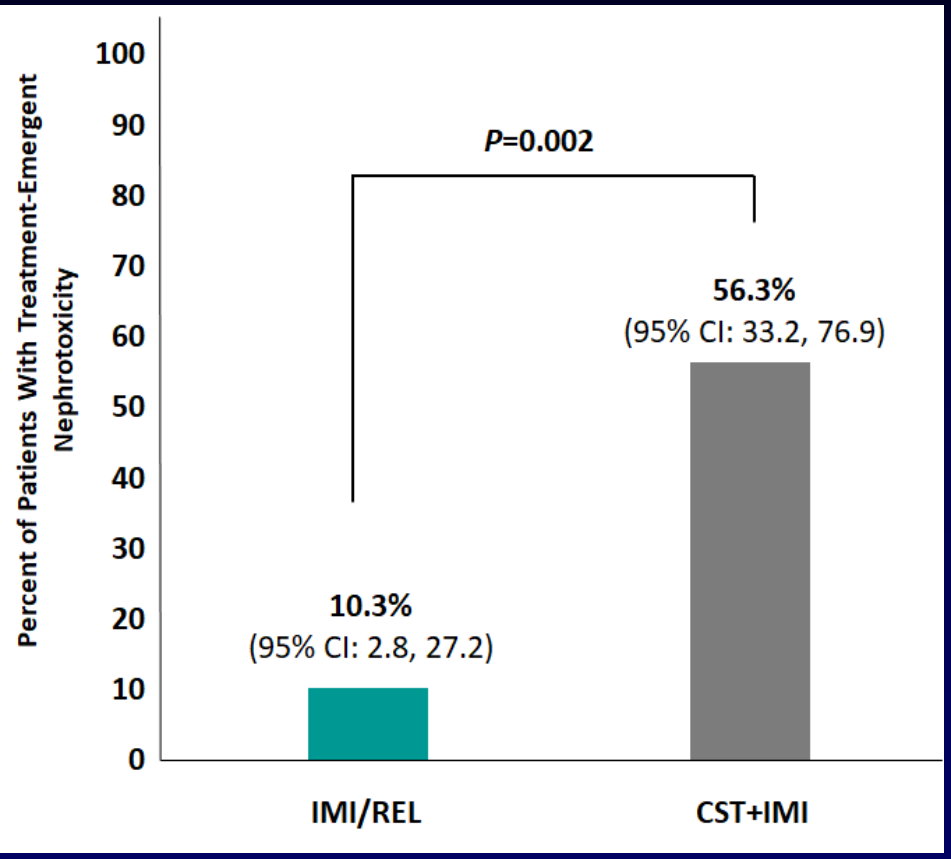


Effect of REL on IMI Susceptibility of ESBL- and Amp-C-Expressing Enterobacteriaceae

Increased susceptibility to IMI from 94% in the absence of REL to 97% in presence of 4 mg/L REL
N=6406 from SMART surveillance 2016



RESTORE-IMI 1: Nephrotoxicity



Criteria for AKI

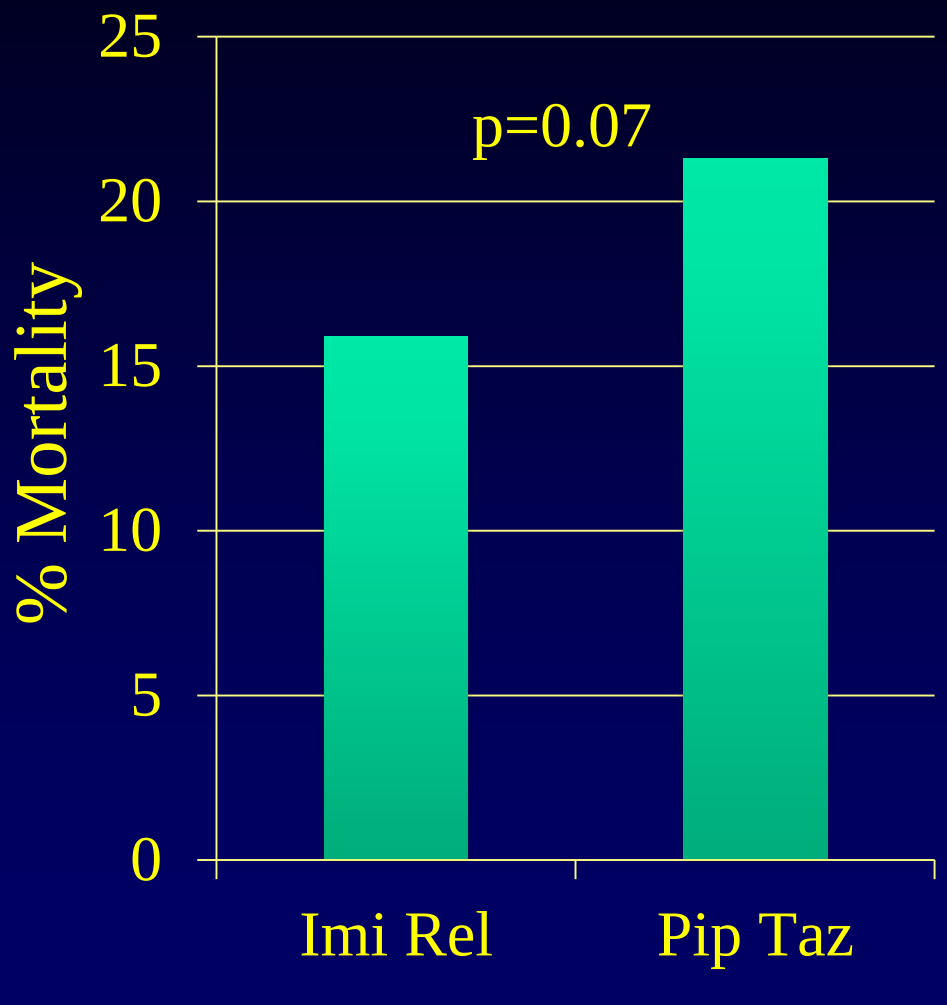
- Treatment-emergent nephrotoxicity was assessed by protocol-defined criteria:
  - In participants with normal baseline renal function (serum creatinine [Cr] <1.2 mg/dL)
    - Doubling of serum Cr up to >1.2 mg/dL or ≥50% reduction in creatinine clearance (CrCL)
  - In participants with pre-existing renal dysfunction (serum Cr ≥1.2 mg/dL),
    - Increase in serum Cr by ≥1 mg/dL, ≥20% reduction in CrCL, or need for renal replacement therapy

Nephrotoxicity by guideline-based definitions of AKI

	IMI/REL		CST+IMI	
	n/m	% (95% CI)	n/m	% (95% CI)
Protocol-defined nephrotoxicity	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)
AKI (KDIGO)	n/m	%	n/m	%
Stage 1	5/29	17.2	6/16	37.5
Stage 2	1/29	3.4	2/16	12.5
Stage 3	0/29	0	5/16	31.3
AKI (RIFLE)	n/m	%	n/m	%
Risk	3/29	10.3	6/16	37.5
Injury	2/29	6.9	2/16	12.5
Failure	0/29	0	4/16	25.0

Restore Imi 2

- -DBRCT
- -Interventions
- --Imi/Rel 500mg/500mg q6
- --Pip/taz 4.5 gm q6
- -Stratified by
- -- Pneumonia type
- -- APACHE II score
- -n=526
- -Primary endpoint
- -- 28 d all cause mortality



Titov I, et al CID. Published online 12 Aug 2020.

MAGIC BULLET

Stopped early due to excess nephrotoxicity in colistin arm

- Magic Bullet: Open label RCT of colisitn (4.5 mil load followed by 3 mil q8)vs meropenem (2g IV q8)
- n=235
- Most common pathogens
  - *A. bummani* 16%
  - *P. aeruginosa* 16%
  - *K. pneumonia* 14%
  - *E. coli* 9%
- 38% were carbapenem resistant, 12% colistin resistant

	Colistin	Meropenem	p
28 d Mortality	22.5%	21.4%	0.75
Clinical Cure	68.3%	72.3%	0.51
Renal Replacement Therapy	9.1%	1.7%	0.01

Cisneros JM, et al. Crit Care 2019; 23: 383.

MAGIC BULLET: Impact of Resistance on Outcomes

Table 4 Twenty-eight-day mortality per pathogen minimum inhibitory concentration (MIC) in the 79 episodes of *A. baumannii*, *P. aeruginosa*, or *K. pneumoniae* isolated in respiratory samples obtained at baseline

	Colistin + levofloxacin group ($n = 120$), death/total number of cases (%)	Meropenem + levofloxacin group ($n = 112$), death/total number of cases (%)	p value
VAP caused by *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* ($n = 79$)	40 (48.8)	39 (52)	0.811
MIC distribution			
Meropenem MIC			
≤ 2 mg/l—susceptible	4/16 (25)	5/18 (27.8)	0.885
> 2–8 mg/l—intermediate	0/4 (0)	0/5 (0)	–
> 8 mg/l—resistant	5/20 (25)	6/16 (37.5)	0.419
Colistin MIC			
≤ 2 mg/l—susceptible	9/35 (25.7)	8/32 (25)	0.947
> 2 mg/l—resistant	0/5 (0)	3/7 (42.9)	0.091

MIC minimum inhibitory concentration, *VAP* ventilator-associated pneumonia

Activity Targets of Several Novel Agents

Agent	Activity Targets			
	ESBL	CRE	PA	AB
Cefidericol	Yes	Yes	Yes	Yes
Ceftolozane/tazobactam	Yes	No	Yes	No
Imipenem/relebactam	Yes	Yes	Yes	No
Colistin	Yes	Yes	Yes	Yes

ESBL - Extended spectrum producing Enterobacteriacae; CRE – Carbapenem resistant Enterobacteraciae; PA – P. aueruginosa; AB = Acinetobacter

Spectrum of Beta-Lactamase Activity

Spectrum	Agent			
	Cefidericol	Ceftolozane/ Tazobactam	Imipenem/ Relebactam	Colistin
Class A narrow-spectrum	X	X	X	X
Class A ESBLs	X	X	X	X
Class A carbapenemases	X		X	X
Some class C enzymes	X	X	X	X
Some class D enzymes	X			X

Conclusions

- Resistance among GNR increasing
- Pattern seen globally and in multiple pathogen types
- Resistance drives inappropriate therapy
- We know very little about how to use antibiotics in the patients who need them most urgently