Pharmacodynamics as an Approach to Optimizing Therapy Against Problem Pathogens

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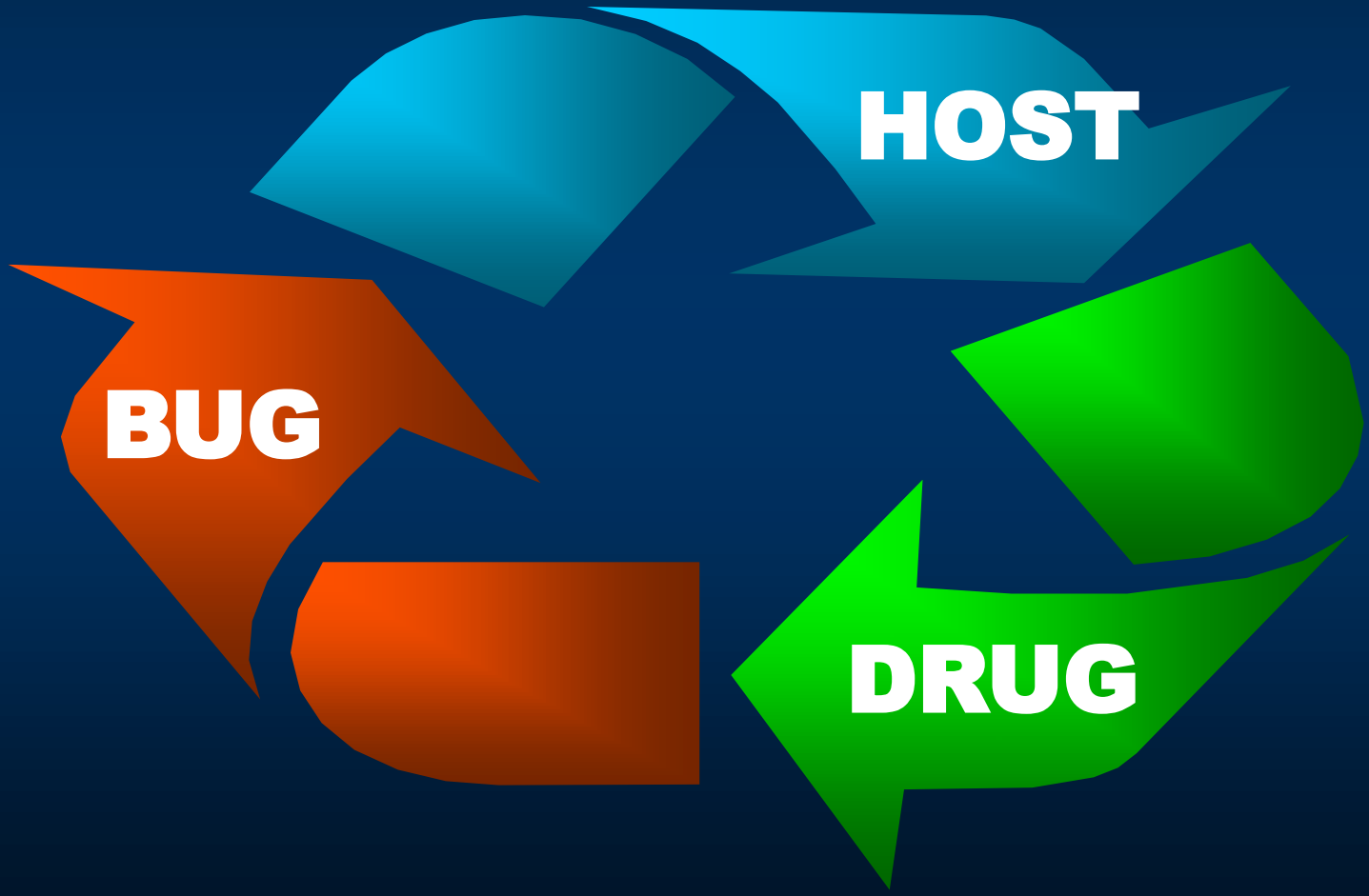
Learning Objectives

- List current trends in antibiotic resistance and new drug development
- Discuss general concepts of pharmacokinetics and pharmacodynamics
- Apply pharmacodynamics to optimize dosing regimens for beta-lactams and aminoglycosides
- Identify drug options for multi-drug resistant gram-negative bacteria

Improving the Probability of Positive Outcomes

IMPROVING THE ODDS



Nicolau DP Am J Man Care 1998:4(10 Suppl) S525-30

Problematic Gram-Negatives in the Hospital Setting and Mechanisms of Resistance

- *Pseudomonas aeruginosa*
  - AmpC production, efflux pumps (Mex*AB*-Opr*M*, etc), outer membrane porin changes (i.e., loss of Opr*D*), Metallo-Beta-Lactamase production (e.g., bla_{VIM}, bla_{IMP}), *gyrA*/*parC* mutations, aminoglycoside-modifying enzymes (AME), ESBL/KPC production (more recent)

- *Acinetobacter* species
  - AmpC, ESBL (TEM-1, SHV-type, CTX-M-type), and serine (bla_{OXA}) and metallo (bla_{VIM}, bla_{IMP}) carbapenemase production, outer membrane porin changes, AME, *gyrA*/*parC* mutations, efflux pumps

- Enterobacteriaceae (*Klebsiella* species, *E. coli*, *Enterobacter* species)
  - ESBL, Klebsiella-producing-carbapenemase (KPC-2, -3, -4, etc.) production, AmpC, outer membrane porin changes, plasmid mediated quinolone resistance gene (*qnrA*), NDM-1

Bonomo RA, et al. *Clin Infect Dis* 2006;43:S49-56
Nicasio AM, et al. *Pharmacother* 2008;28:235-49

Risk factors for infection with Multidrug-resistant (MDR) pathogens

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community
- High frequency of antibiotic resistance in the specific hospital unit
- Requiring ventilator support
- Immune-suppressive illness (including treatment with corticosteroids)

ATS/IDSA. *Am J Resp Crit Care Med* 2005;171:388-416.

Bad Bugs, No Drugs

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews

www.idsociety.org/WorkArea/showcontent.aspx?id=5554

Bad Bugs, No Drugs
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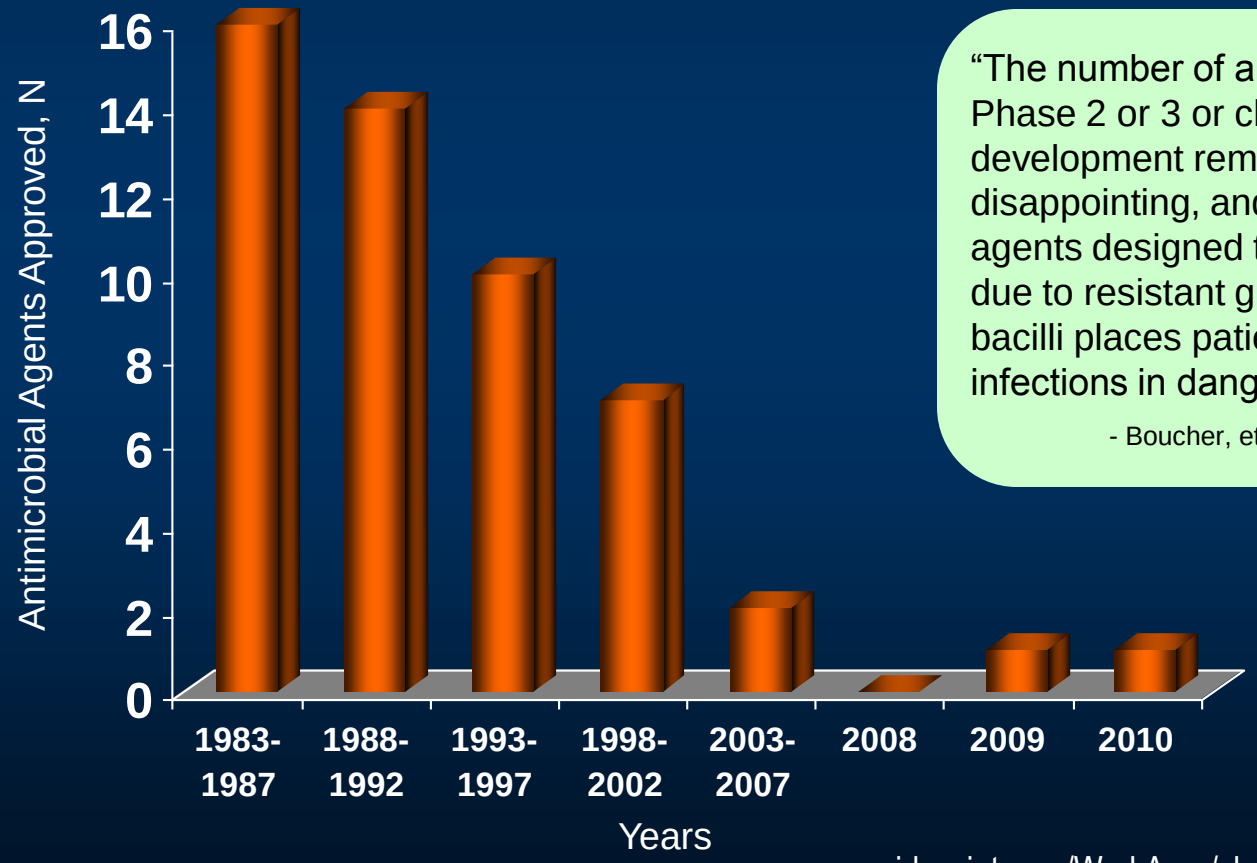


"The number of antibacterials in Phase 2 or 3 or clinical development remains disappointing, and the absence of agents designed to treat infections due to resistant gram-negative bacilli places patients with these infections in danger."

- Boucher, et al. Clin Infect Dis 2009

www.idsociety.org/WorkArea/showcontent.aspx?id=5554

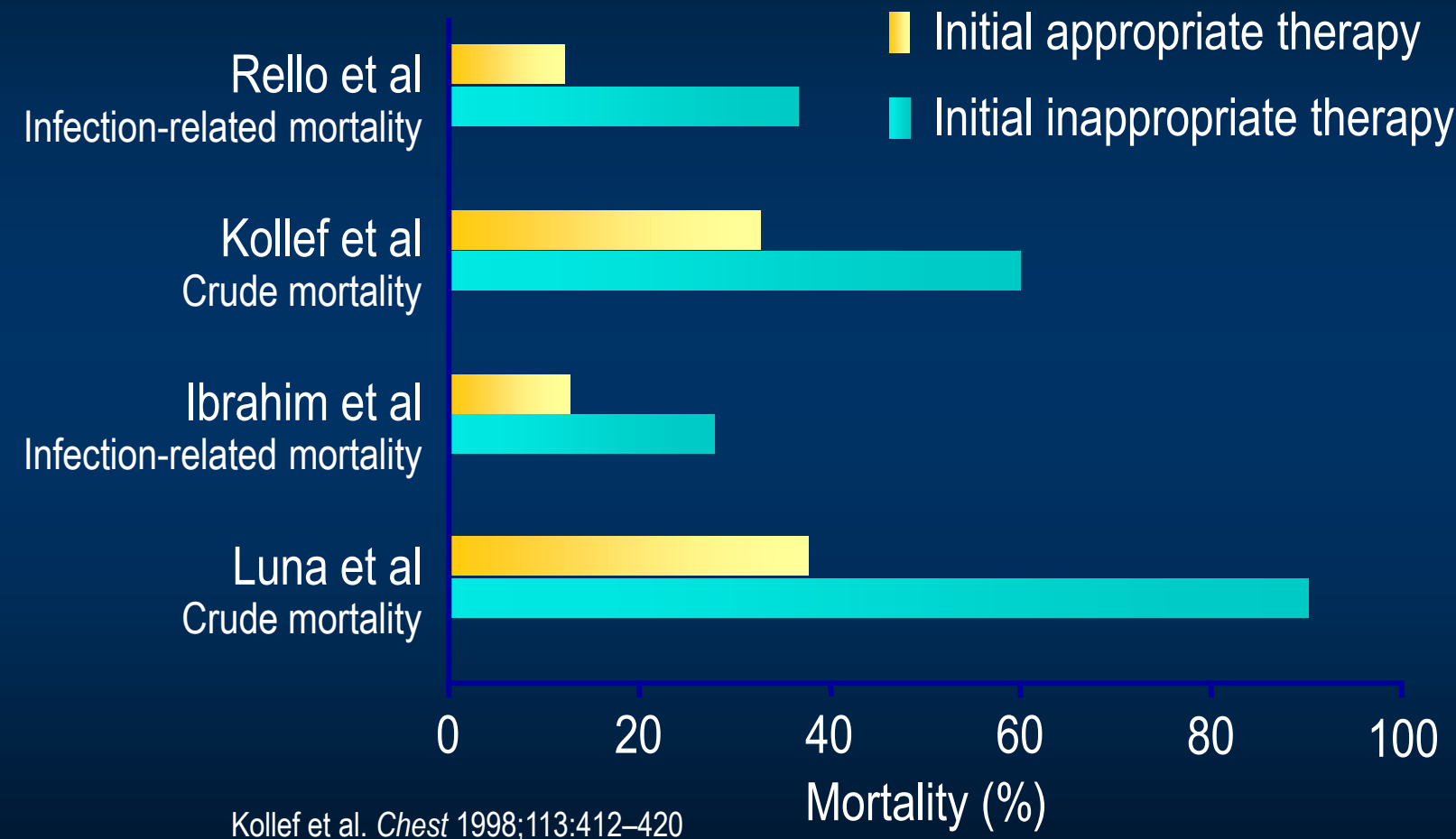
Inadequate Antimicrobial Treatment

- Impact of inadequate empiric therapy
  - Increased mortality
  - Increased ICU LOS (10.2 vs 7.1 days)
  - Increased duration of mechanical ventilation (11.1 vs 7.6 days)
  - Greater number of organ system derangements
  - Increased risk of septic shock and bacteremia

LOS=length of stay.

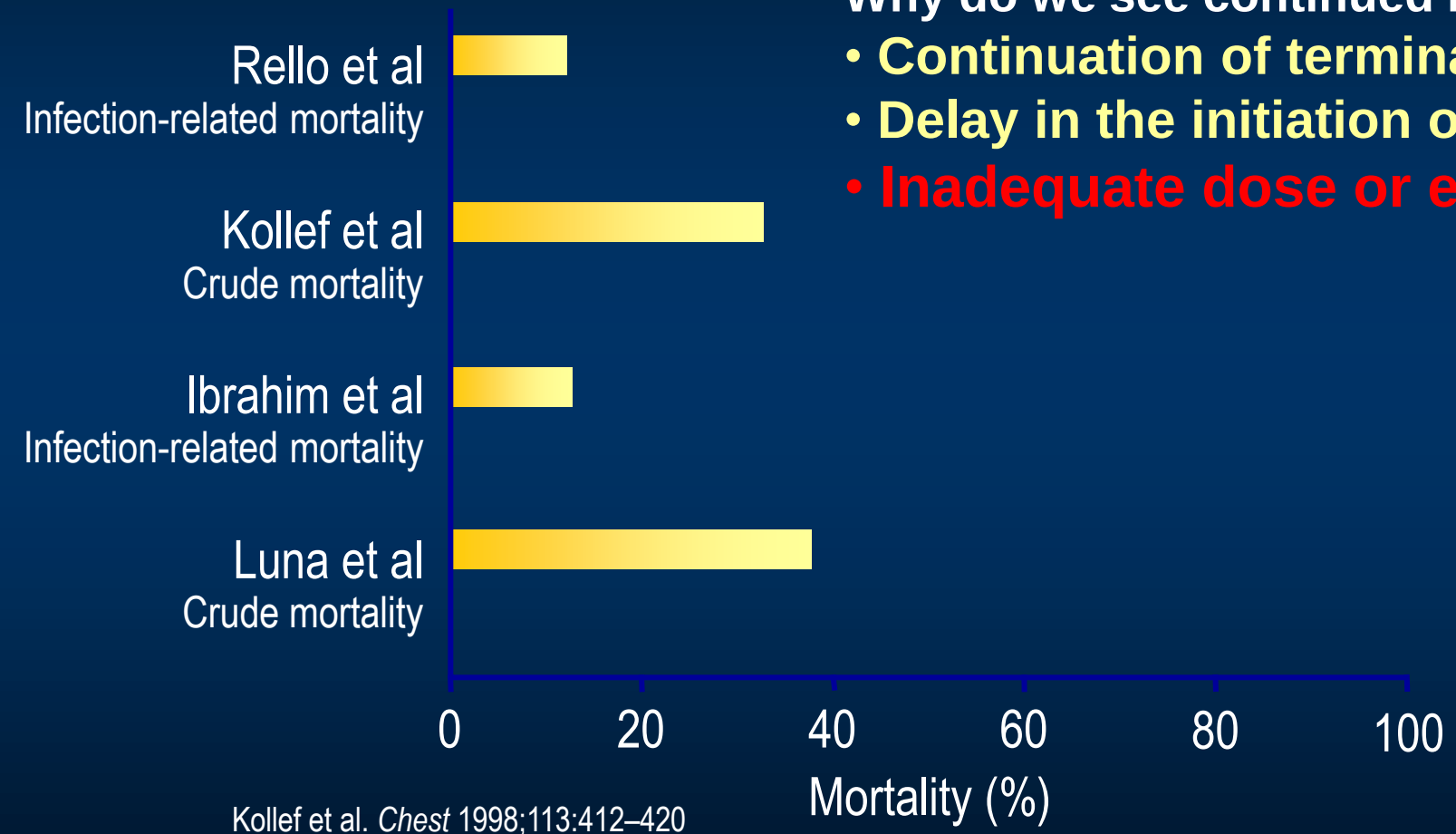
Kollef MH et al. *Chest*. 1999;115:462-474.

Mortality associated with initial inappropriate therapy



Kollef et al. *Chest* 1998;113:412–420
Ibrahim et al. *Chest* 2000;118:146–155
Luna et al. *Chest* 1997;111:676–685
Rello et al. *Am J Respir Crit Care Med* 1997;156:196–200

Mortality associated with initial inappropriate therapy



Why do we see continued Mortality?

- **Continuation of terminal process**
- **Delay in the initiation of therapy**
- **Inadequate dose or exposure?**

Kollef et al. *Chest* 1998;113:412–420
Ibrahim et al. *Chest* 2000;118:146–155
Luna et al. *Chest* 1997;111:676–685
Rello et al. *Am J Respir Crit Care Med* 1997;156:196–200

Do We Deliver Effective Doses in Critically Ill Patients: Empiric Therapy

- Pharmacodynamic goal not achieved in 16/19 (84%)
  - 8/16 (50%): organism resistant to empiric therapy
  - 8/16 (50%): organism susceptible…but therapy not optimal
    - 6/8 organisms had MIC's at the breakpoint
    - 2/8 organisms had MIC's 1 dilution below the breakpoint

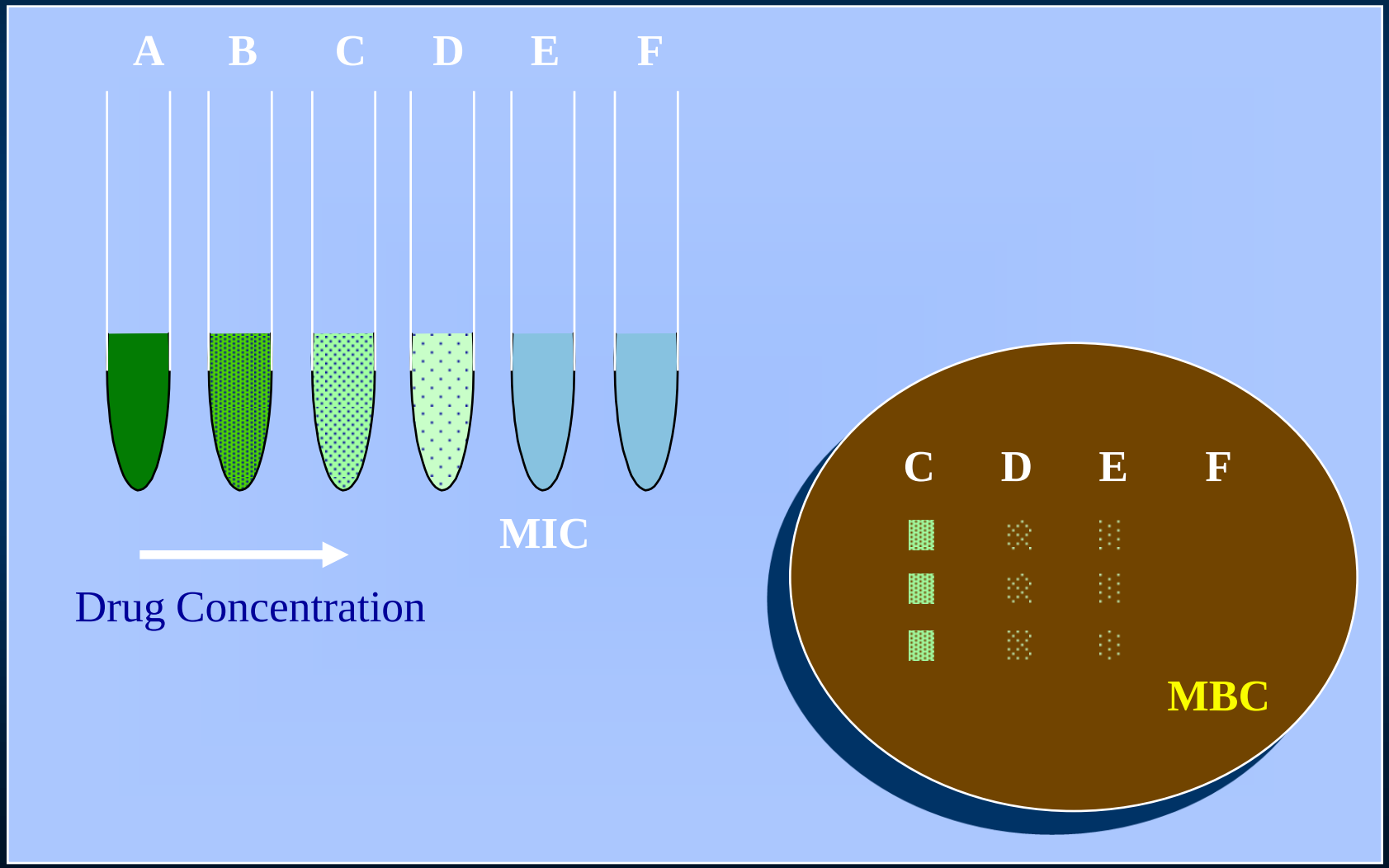
Mohr JF, et al. *Diagn Micro Infect Dis* 2004;48:125-30.

What Are the Goals of PD Optimization?

- Modify dosing to fit the patient (PK) and pathogen (minimum inhibitory concentration [MIC])
- Maximize outcomes
- Minimize potential toxicity
- Limit resistance
- What information is required to optimize dose selection?
  - Exposure target: what do you wish to achieve?
  - Target pathogen MIC distributions
  - Protein binding
  - Human population pharmacokinetics

Determination of Microbiologic Potency: Static & Bactericidal Activity

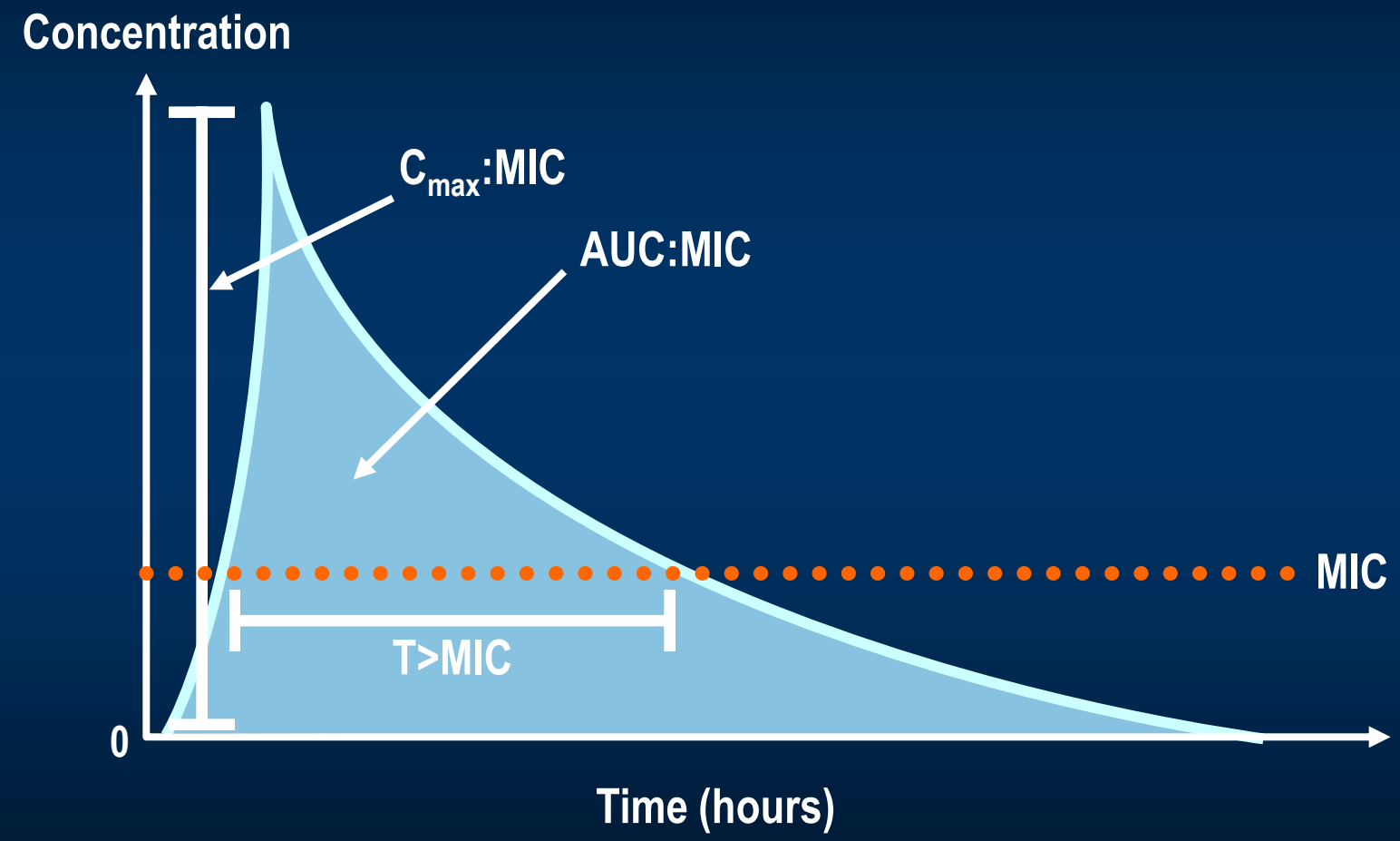
Broth Macro/Microdilution Method



Clinical Susceptibility Breakpoints

- CLSI in USA
  - “The committee is an international, interdisciplinary, non-profit, standards developing, and educational organization.”
  - S, I, R
- EUCAST in EU

Pharmacodynamic parameters



AUC = Area under the concentration–time curve

C_{max} = Maximum plasma concentration

Pharmacodynamic parameters predictive of outcome

	C_{max}:MIC	AUC:MIC	T>MIC
Examples	Aminoglycosides Fluoroquinolones	Azithromycin Fluoroquinolones Ketolides Linezolid Daptomycin Vancomycin Tigecycline	Carbapenems Cephalosporins Macrolides Monobactams Penicillins
Organism kill	Concentration-dependent	Concentration-Dependent or Time Dependent	Time-dependent
Therapeutic goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

Drusano & Craig. *J Chemother* 1997;9:38–44
Drusano et al. *Clin Microbiol Infect* 1998;4 (Suppl. 2):S27–S41
Vesga et al. 37th ICAAC 1997

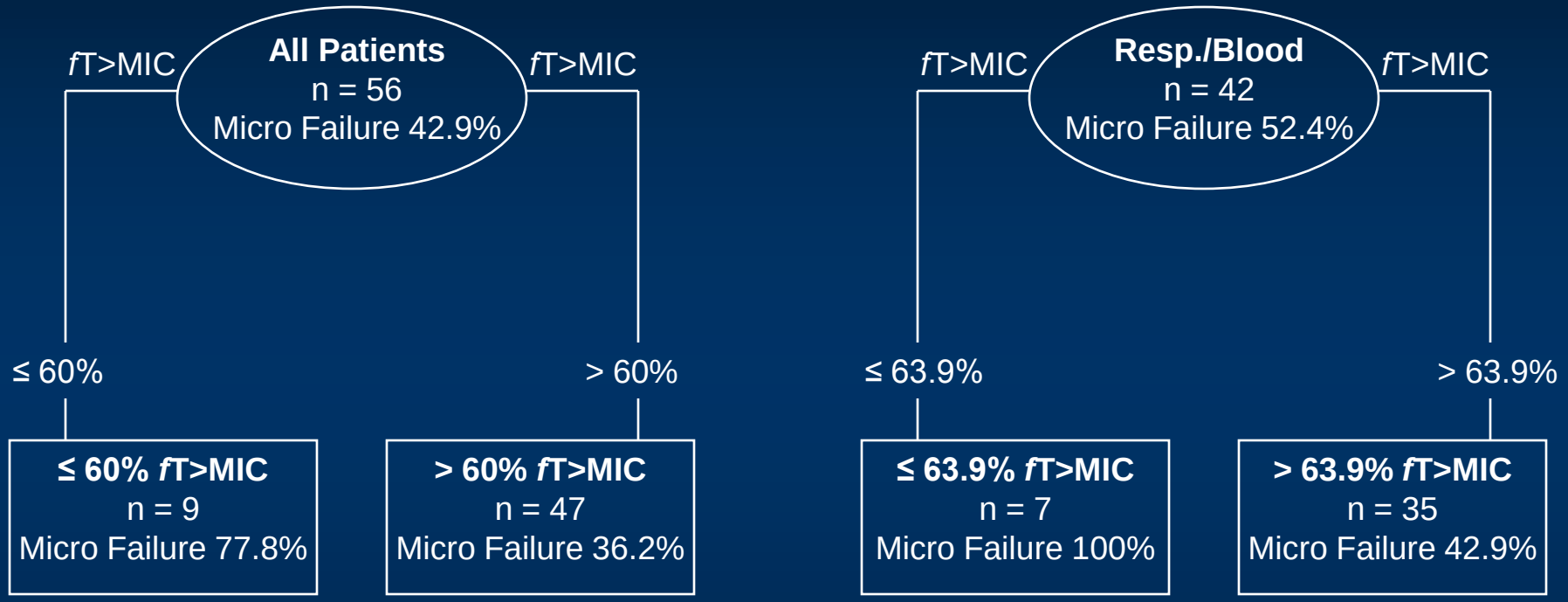
Beta-lactam Pharmacodynamics

	% T> MIC*	
	Bacteriostatic (%)	Bactericidal† (%)
Cephalosporins	35-40	60-70
Penicillins	30	50
Carbapenems	20	40

* Percentages relate to free drug concentration time greater than MIC
† 2-3log reduction in colony forming units.

Drusano GL. *Nature Reviews/ Microbiology.* 2004;2:289-300.
Craig WA *Clin Infec Dis* 1998;26:1-12.
Zhanel G, et al. *Drugs* 2007;67:1027-52.

Clinical Pharmacodynamic Parameter Partitioning for Cefepime vs. *P. aeruginosa*



Crrandon, JL et al. *Antimicrob Agents Chemother* 2010;54:1111-16

Multiple Logistic Regression* for Microbiological Failure

Total Population

Hosmer-Lemeshow Statistic: 3.598 (p=.463)

Variable	*Microbiological Failure*	
	OR (95% CI)	*p-value*
≤ 60% *f*T>MIC	8.10 (1.18 – 55.57)	0.033
Combination Therapy	2.15 (0.59 – 7.88)	0.247
SSSI	0.18 (0.03 – 1.19)	0.074

*Tested variables included creatinine clearance, immunosupression, respiratory infection, SSSI, combination therapy, and *f*T>MIC ≤ 60%

Monte Carlo Simulation

- Stochastic simulation tool
  - Choose dosage regimens for further clinical development
  - Determination of tentative susceptibility breakpoints
  - Compare pharmacodynamic profiles of antibiotics to guide therapeutics

Bradley JS, et al. *Ped Infect Dis J.* 2003;22:982-992.

Drusano GL, et al. *Antimicrob Agents Chemother*. 2001;45:13-22.

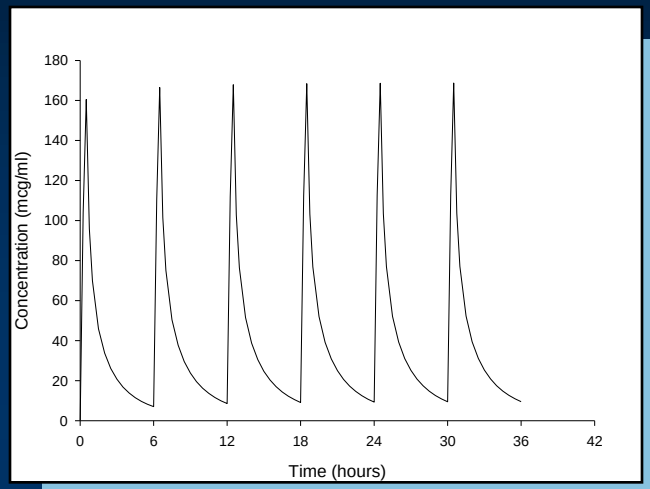
Mouton JW, et al. *Antimicrob Agents Chemother*. 2004;48:1713-1718.

Kuti JL, et al. *Antimicrob Agents Chemother*. 2004;48:2464-2470.

What Information Is Gained From MCS

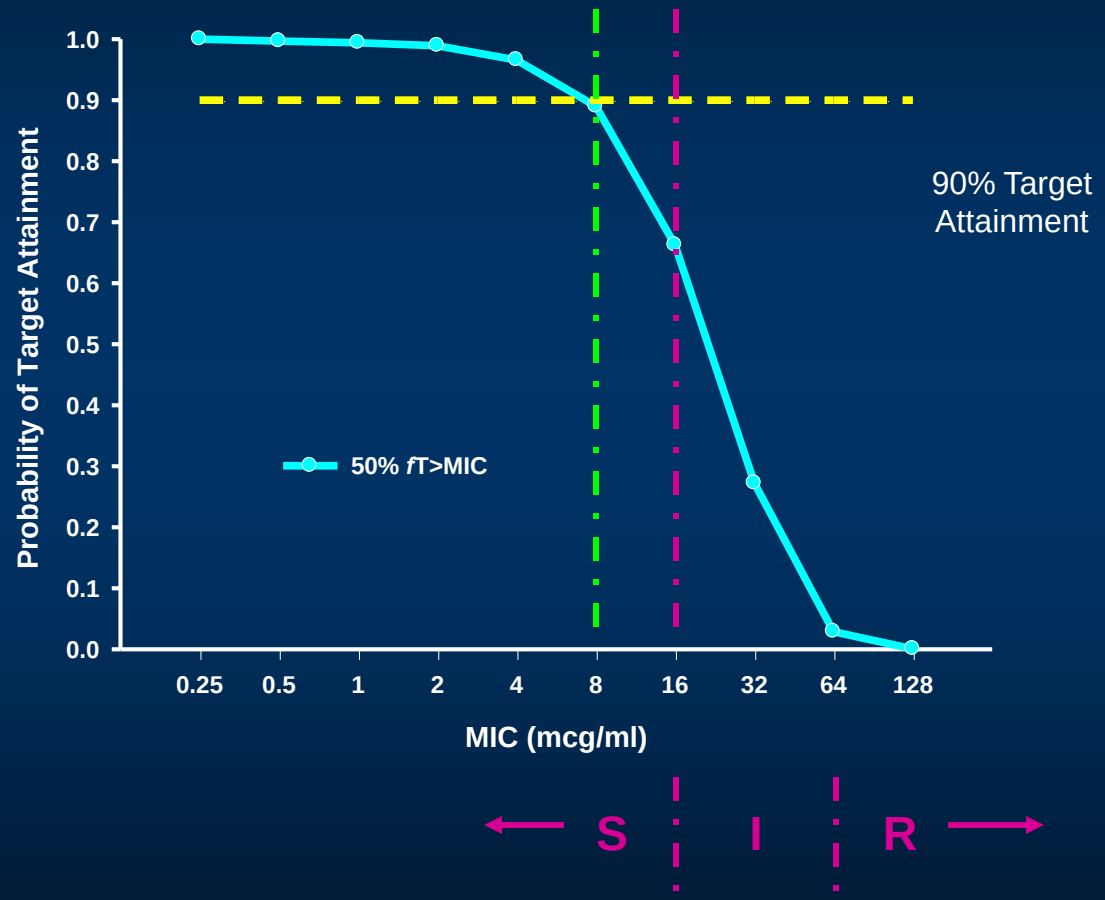
- Probability of Target Attainment (PTA):
  - Proportion of the population that achieves the target level of the pharmacodynamic exposure at each MIC
- Cumulative Fraction of Response (CFR):
  - For each MIC dilution across the distribution, the regimen's PTA was multiplied by the percentage of isolates found at that MIC
  - The sum of these products represents the CFR for the modeled regimen against the MIC distribution from the contributed isolates
  - Provides the likelihood (as %) that a regimen will achieve PD target for a population of isolates

Pharmacodynamic Attainment of Pip/Tazo 3.375g q6h (0.5)



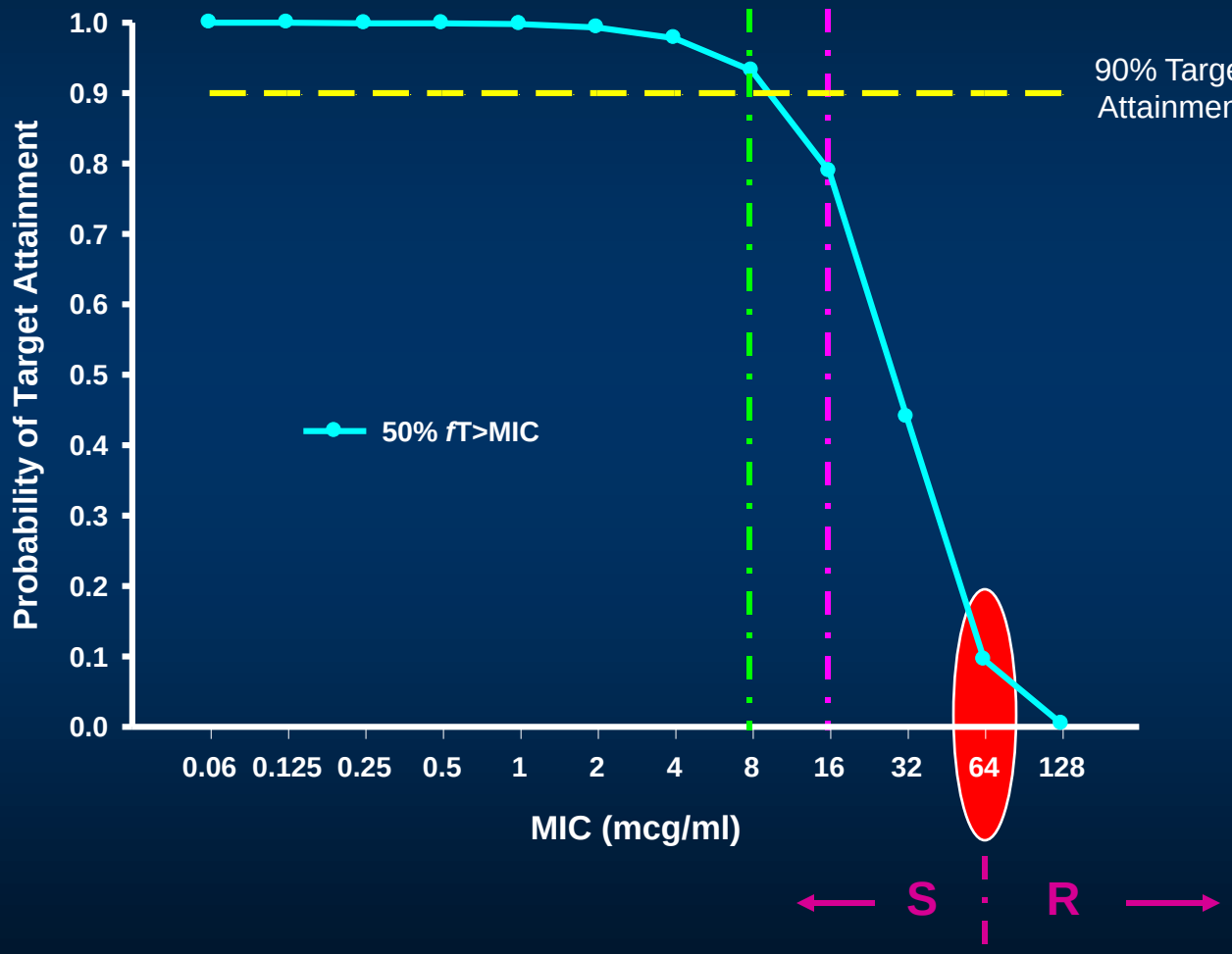
5000 patient Monte Carlo simulation

	Mean (sd)	Covariance			
		Vc	CL	K12	K21
Vc	9.57 (6.57)	43.2			
CL	10.5 (4.73)	11.3	20.4		
K12	2.87 (3.9)	-7.5	0.791	14.9	
K21	2.79 (4.93)	1.58	0.019	8.8	18.9



Lodise TP, et al. *Antimicrob Agents Chemother* 2004;48:4718-24.
DeRyke CA, et al. *Diagn Microbiol Infect Dis* 2007;58:337-44.

Pharmacodynamic Attainment of Pip/Tazo 4.5g q6h (0.5)



DeRyke CA, et al. *Diagn Microbiol Infect Dis* 2007;58:337-44.

Piperacillin/tazobactam Failures versus Bacteremic *Pseudomonas aeruginosa*

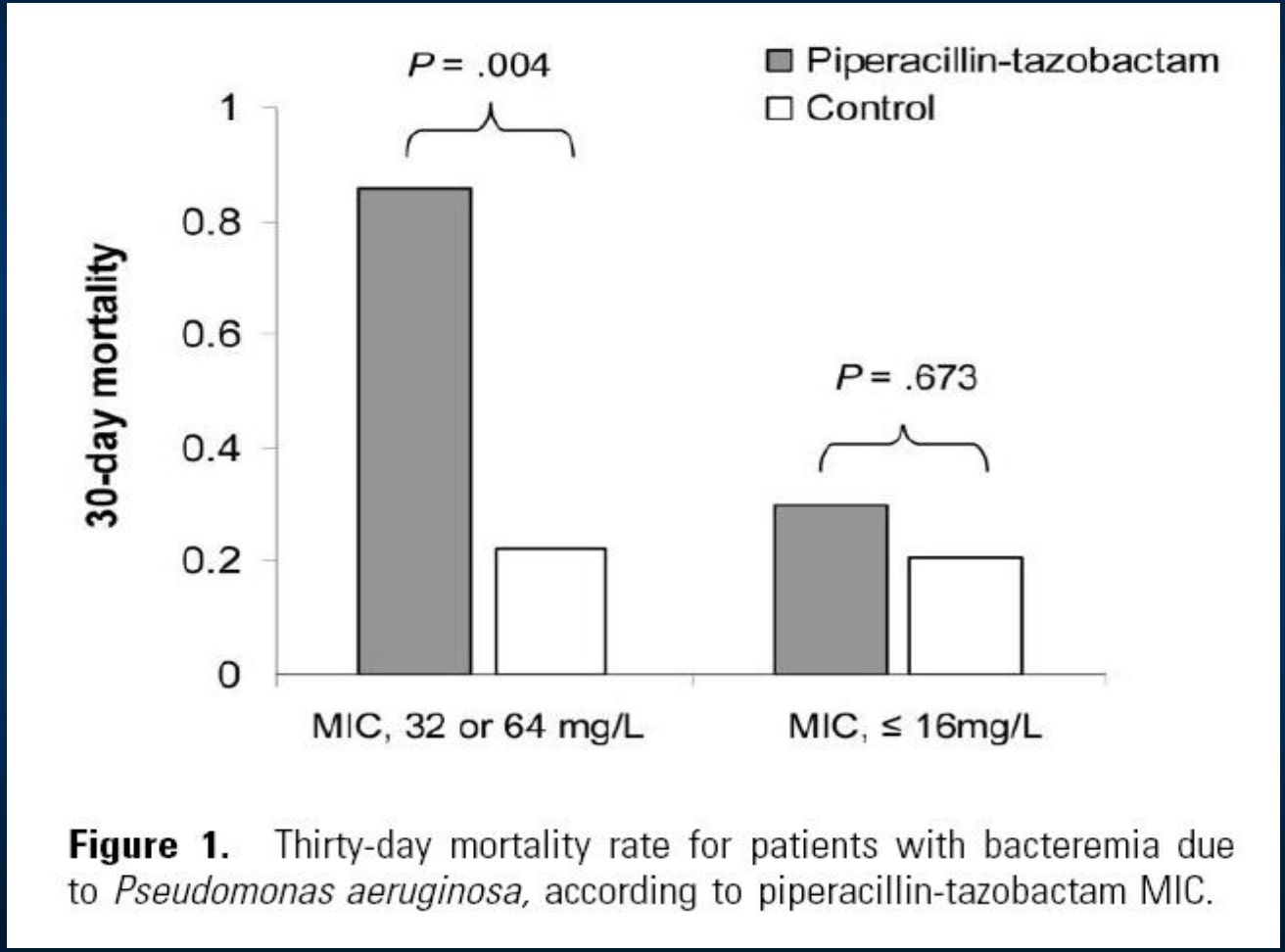
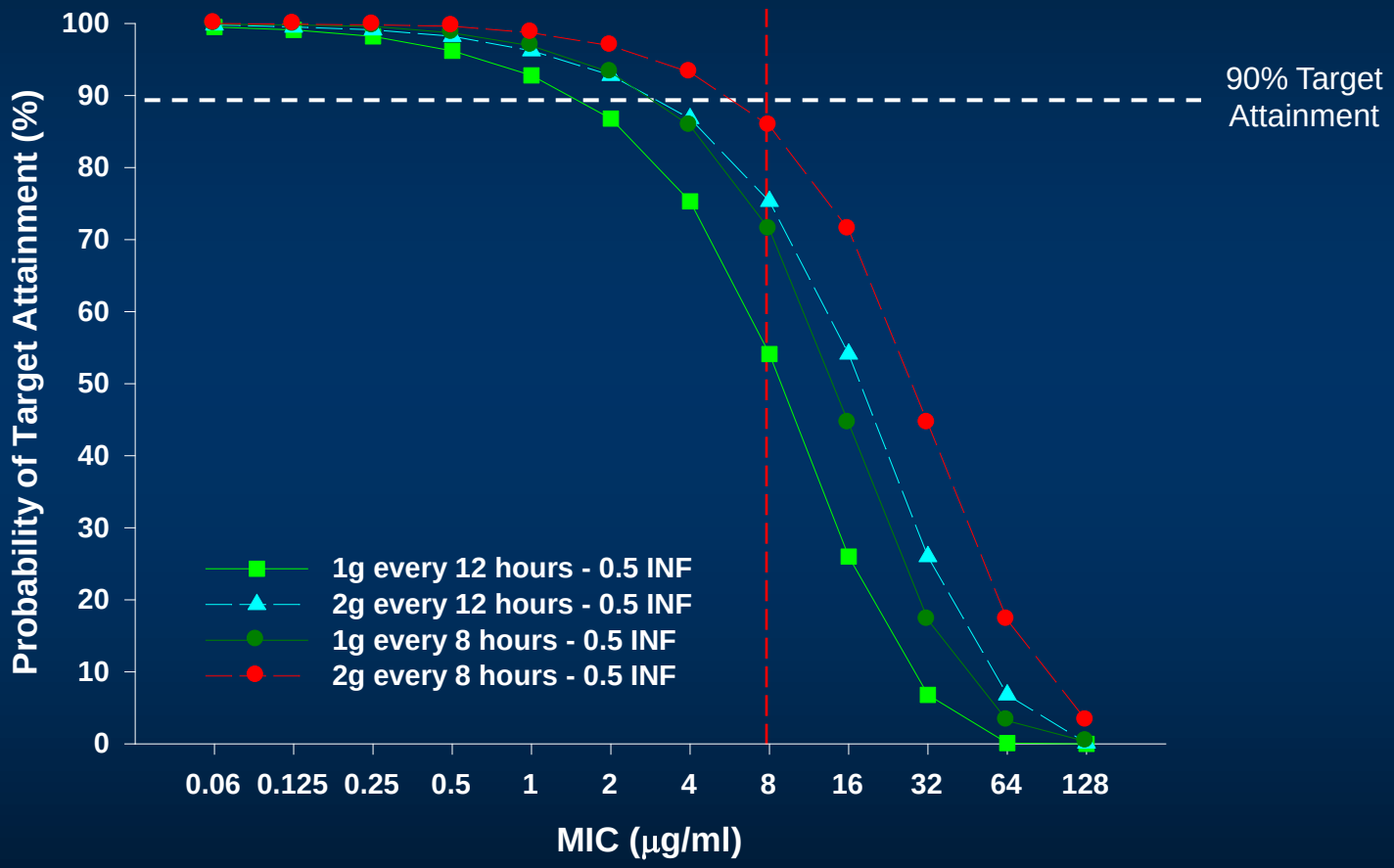


Figure 1. Thirty-day mortality rate for patients with bacteremia due to *Pseudomonas aeruginosa,* according to piperacillin-tazobactam MIC.

Tam VH, et al. *Clin Infect Dis* 2008;46:862-7.

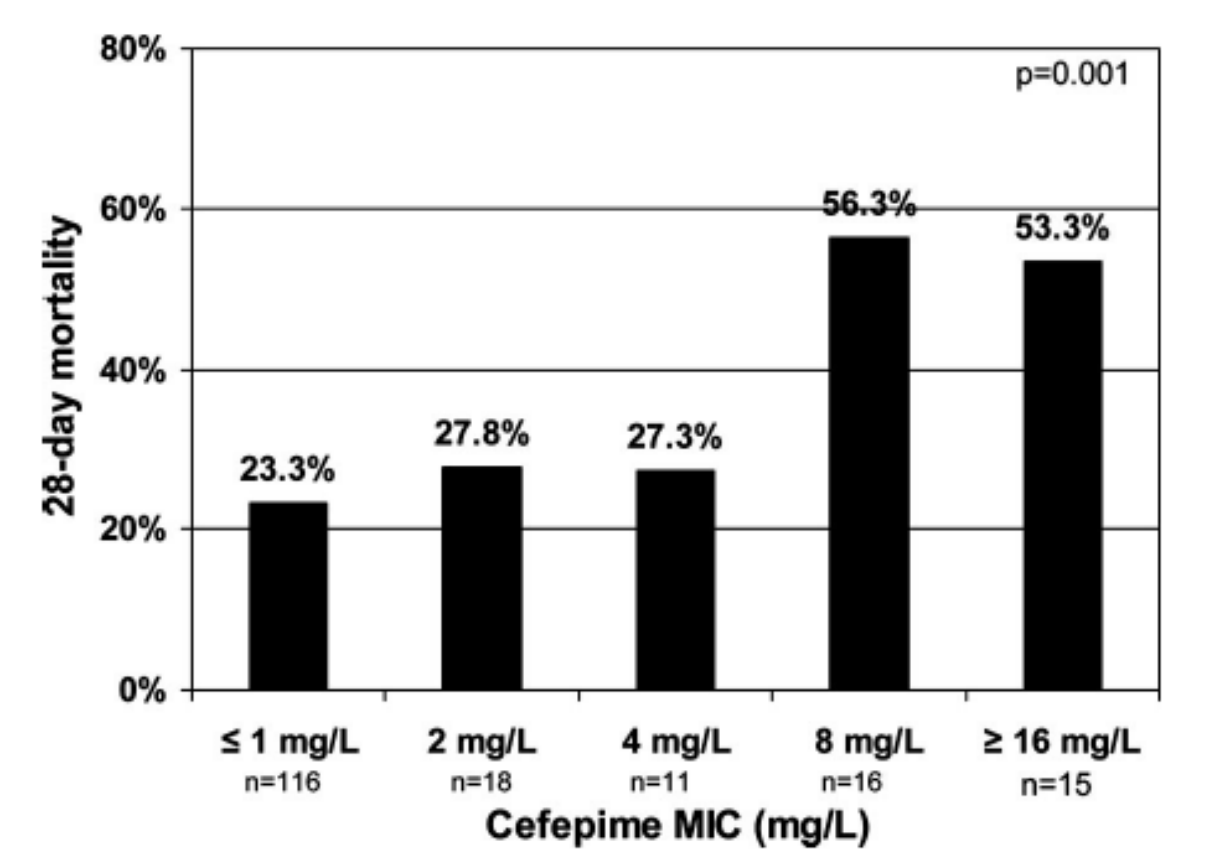
Cefepime Pharmacodynamics

Probability of achieving 50% *f*T>MIC for VAP patients (CrCL: 50ml/min – 120ml/min)



Nicasio AM, et al. *Antimicrob Agents Chemother* 2009;53:1476-81.

Cefepime Mortality for Gram-Negative Bacteremia as a Function of MIC



Bhat S, et al. Antimicrob Agents Chemother 2007;51:4390-5.

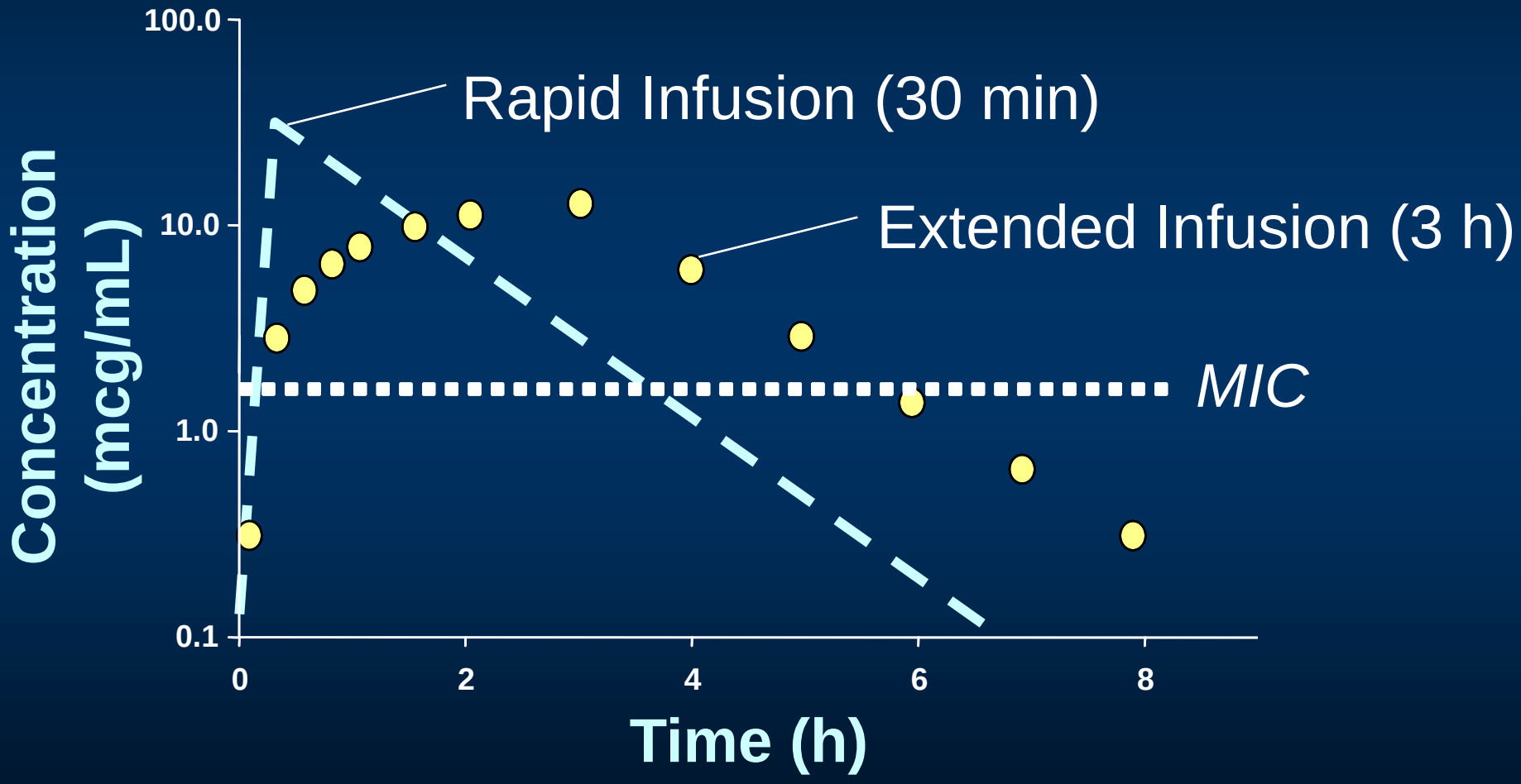
Pharmacodynamic Considerations: Administration Methods to Optimize Exposure

- Concentration Dependent Killers (Cpeak/MIC, AUC/MIC)
  - Higher dose (aminoglycosides, fluoroquinolones)
- Time Dependent Killers (AUC/MIC, T>MIC)
  - Increased dosing frequency (Beta-lactams, fluoroquinolones)
  - Higher dose (Beta-lactams)
  - Increase the duration of infusion (Beta-lactams)
    - Prolonged infusion

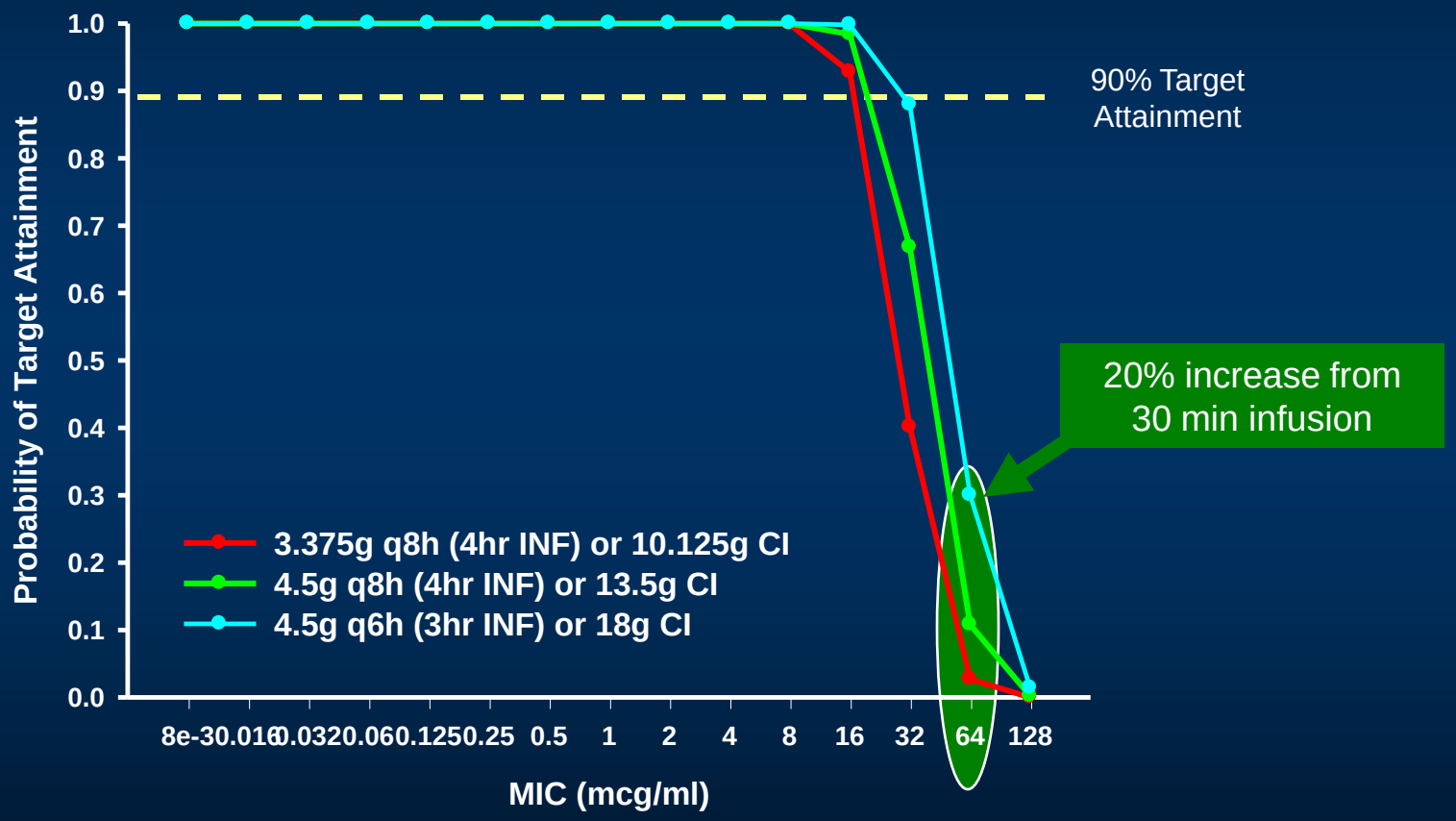
      Same dose and dosing interval, however, change duration of infusion (0.5 hr → 3hr)
    - Continuous infusion

      Administer loading dose, then use pump to give total daily dose IV over 24 hr period

Prolonging the Infusion to Maximize T>MIC



Probability of Bactericidal Exposure for Prolonged or Continuous Infusion Regimens of Piperacillin/tazobactam

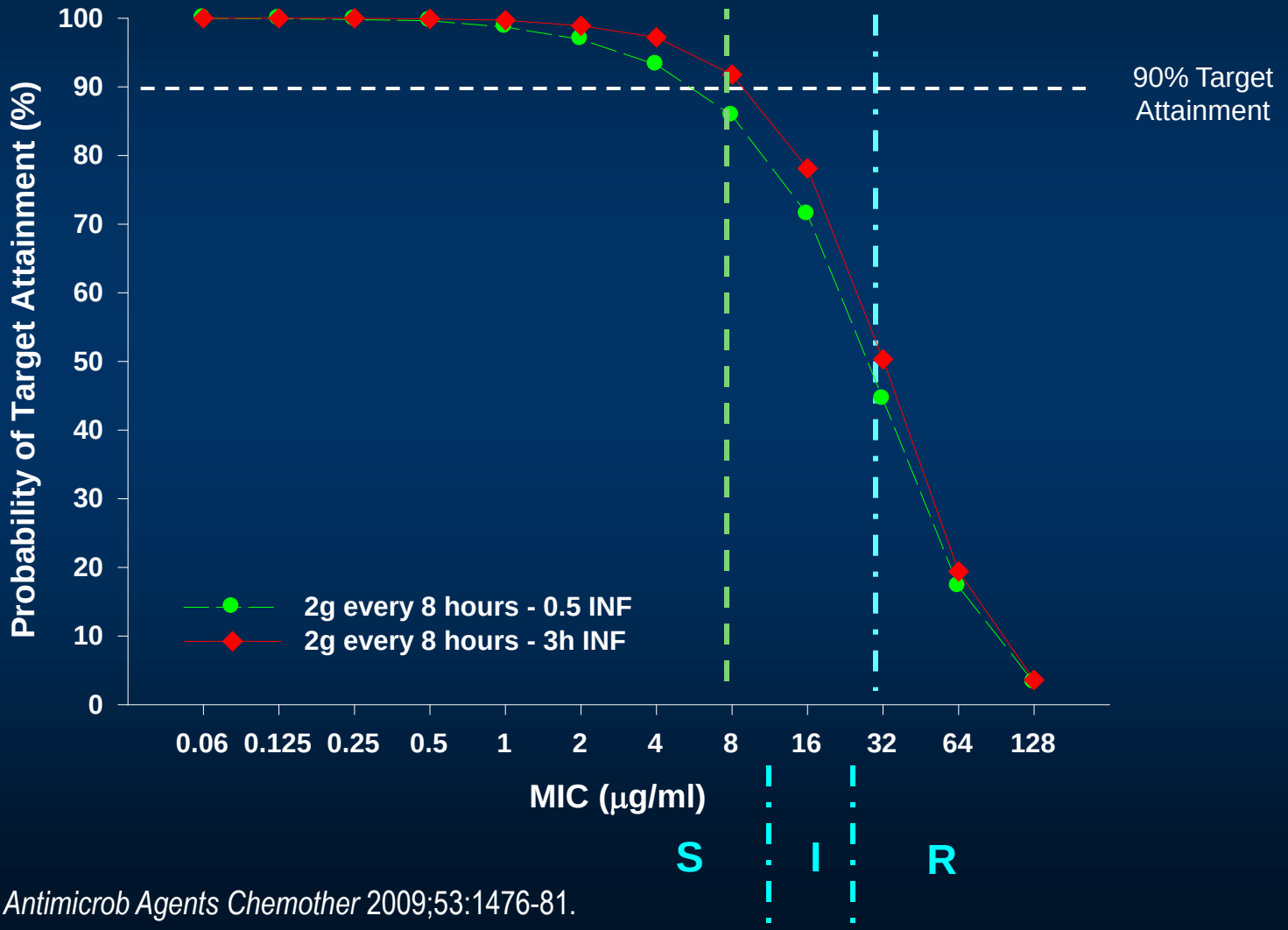


* Bactericidal Exposure defined as 50% *f*T>MIC

Kim A, et al. *Pharmacotherapy* 2007;27:1490-7.

Cefepime 2000mg q8h - 3 hour infusion

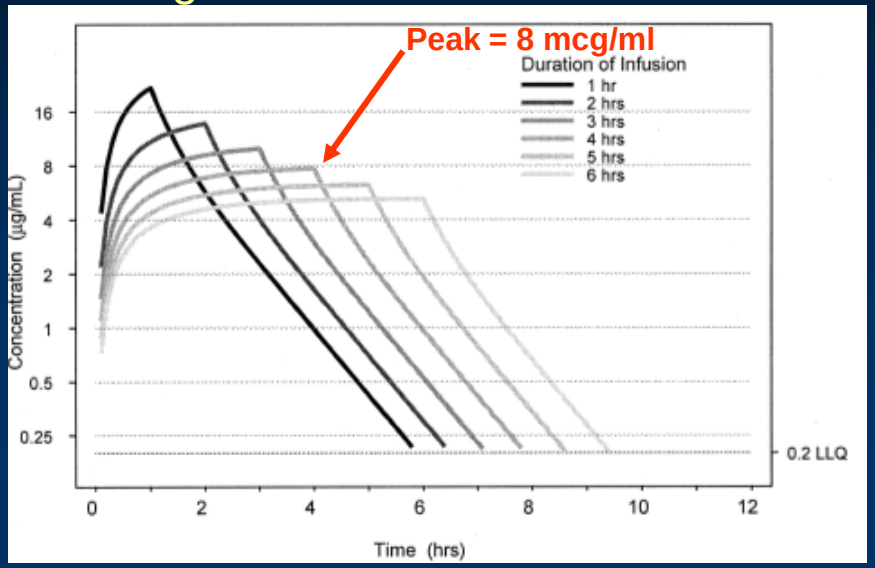
Pharmacokinetics from VAP patients



Nicasio AM, et al. *Antimicrob Agents Chemother* 2009;53:1476-81.

Doripenem Dosing Regimens in Healthy Volunteers with Normal Renal Function

500 mg doses



1000 mg doses

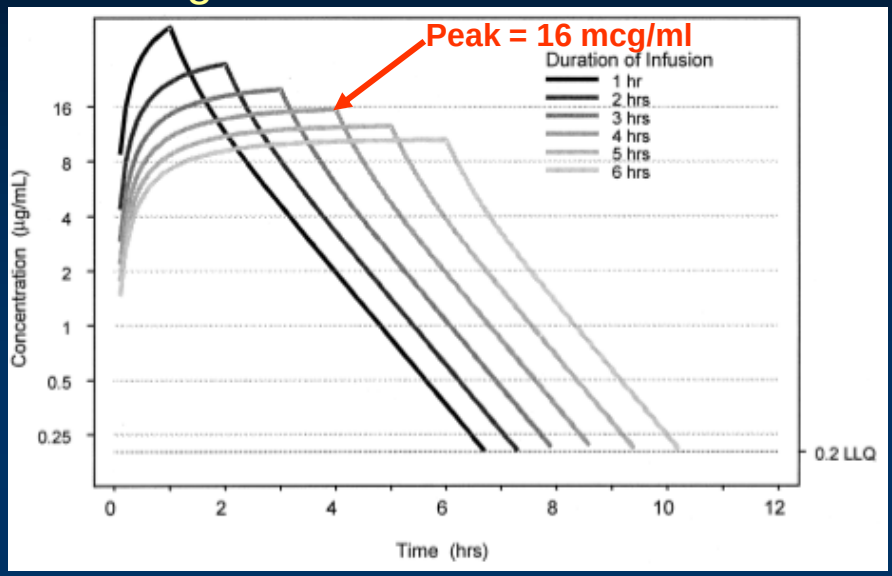


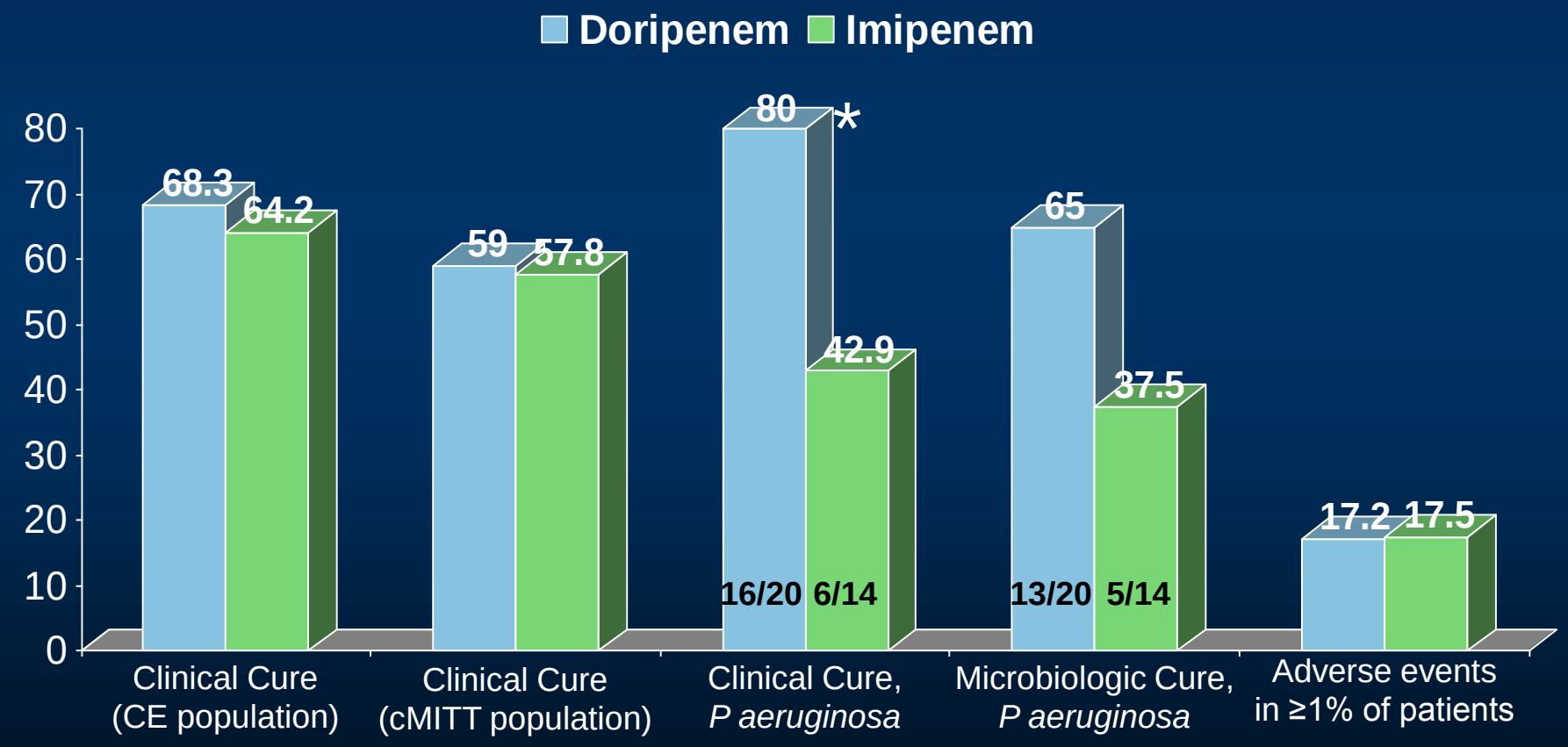
TABLE 2. Comparison of pharmacokinetic-pharmacodynamic target attainment probabilities by dosing regimen, duration of infusion, and MIC

Dosing regimen	Duration of infusion (hr)	MIC (µg/ml)	Probability of patients achieving target T>MIC			
			30%	35%	40%	45%
500 mg q8h	1/2/3	1	1.00/1.00/1.00	1.00/1.00/1.00	1.00/1.00/1.00	0.99/1.00/1.00
500 mg q8h	1/2/3	2	1.00/1.00/1.00	0.99/1.00/1.00	0.77/1.00/1.00	0.25/0.90/1.00
500 mg q8h	3/4/5	4	1.00/1.00/1.00	1.00/1.00/0.99	0.84/0.99/0.99	0.26/0.90/0.95
1,000 mg q12h	4/5/6	4	1.00/1.00/1.00	1.00/1.00/1.00	0.92/1.00/1.00	0.23/0.96/1.00
1,000 mg q8h	1/2/3	4	1.00/1.00/1.00	0.99/1.00/1.00	0.77/1.00/1.00	0.25/0.90/1.00
1,000/2,000/3,000 mg q24h	24	4	0/0.98/1.00	0/0.98/1.00	0/0.98/1.00	0/0.98/1.00
1,000 mg q8h	3/4/5	8	1.00/1.00/1.00	1.00/1.00/0.99	0.84/0.99/0.99	0.26/0.90/0.95
1,000/2,000/3,000 mg q24h	24	8	0/0/0.46	0/0/0.46	0/0/0.46	0/0/0.46

Bhavnani S et al. *Antimicrob Agents Chemother* 2005;49:3944-7.

Doripenem versus Imipenem for Ventilator Associated Pneumonia

- Study design: Open-label, randomized 1:1 (n = 531)
- Study therapy: Doripenem IV 0.5g q8h (4 h) or Imipenem IV 0.5g q6h or 1g q8h
- Length of treatment: 7 to 14 days



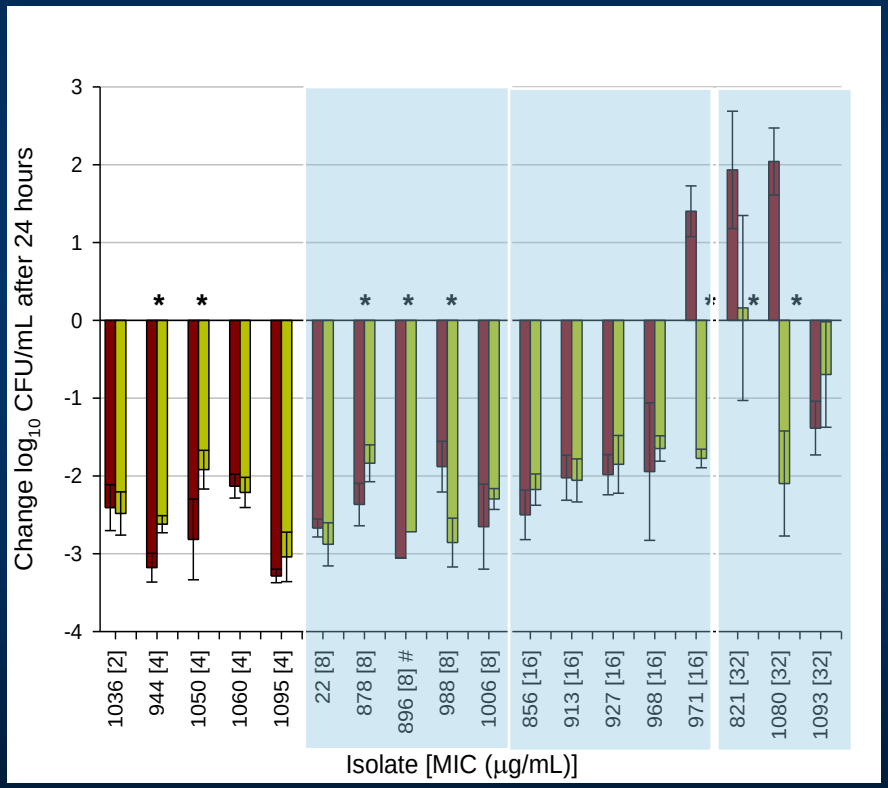
**P* value not significant.

Chastre J ,et al. *Crit Care Med* 2008;36:1089-1096.

Doripenem Pharmacodynamics against *Pseudomonas aeruginosa* with a Range of MICs

- Murine thigh infusion model
- 18 *P. aeruginosa* isolates
  - 15 multidrug resistant
- Human simulated doripenem doses of 1g and 2g every 8 hours (4 hour infusions)

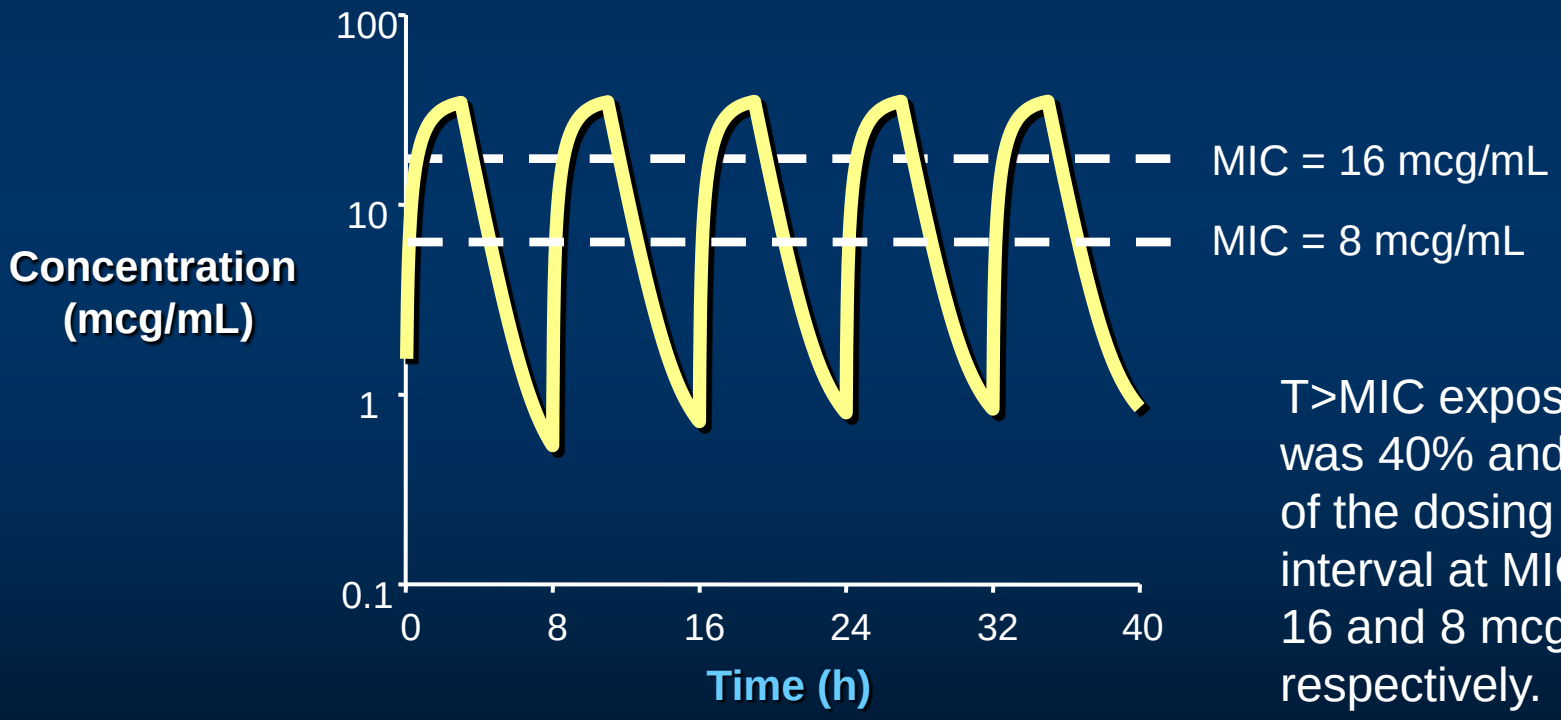
MIC (µg/mL)	Doripenem *f*T>MIC (%)			
	1g 4h infusion		2g 4h infusion	
	Humans	Mice	Humans	Mice
2	80	82.5	95	95
4	65	70	80	82.5
8	50	52.5	65	70
16	0	0	50	52.5
32	0	0	0	0



Crandon JL et al. *Antimicrob Agents Chemother* 2009;53:4352-6.

Treatment of Multidrug Resistant *Burkholderia cepacia* With Prolonged Infusion Meropenem

Meropenem 2 g infused over 3 hours q 8 h



T>MIC exposure was 40% and 52% of the dosing interval at MICs of 16 and 8 mcg/mL, respectively.

Kuti JL, et al. *Pharmacother* 2004;24:1641-5

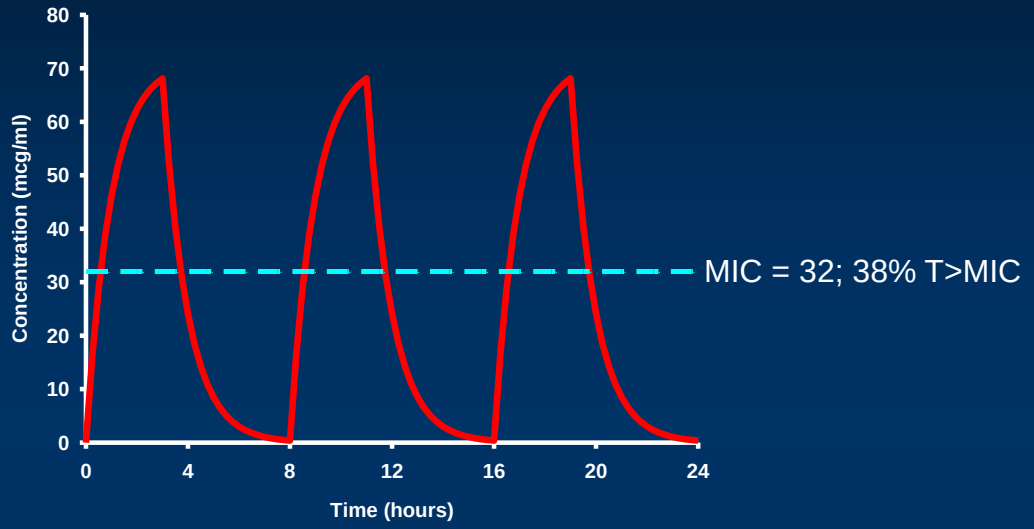
Carbapenem Prolonged Infusion versus Resistant Gram-negatives in Cystic Fibrosis Patients

Meropenem 3g q8h (3 hour infusions)

41 year old female CF with known *B. cepacia* complex (meropenem MIC=32 mcg/ml)

Treated for 14 days with meropenem plus TMP-SMZ

Successful response

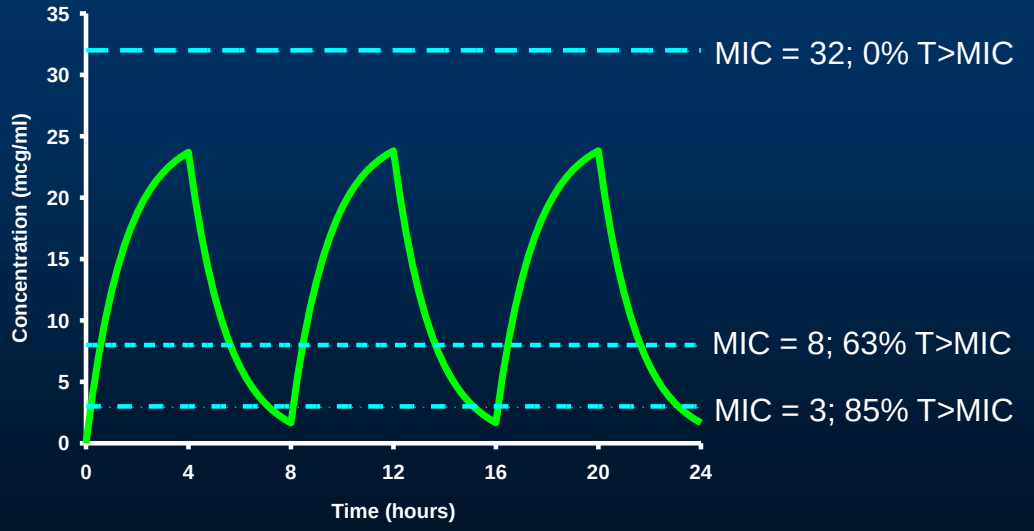


Doripenem 2g q8h (4 hour infusions)

22 year old male CF with three MDR *P. aeruginosa* (doripenem MICs=3, 8, >32 mcg/ml)

Treated for 14 days with doripenem plus tobramycin

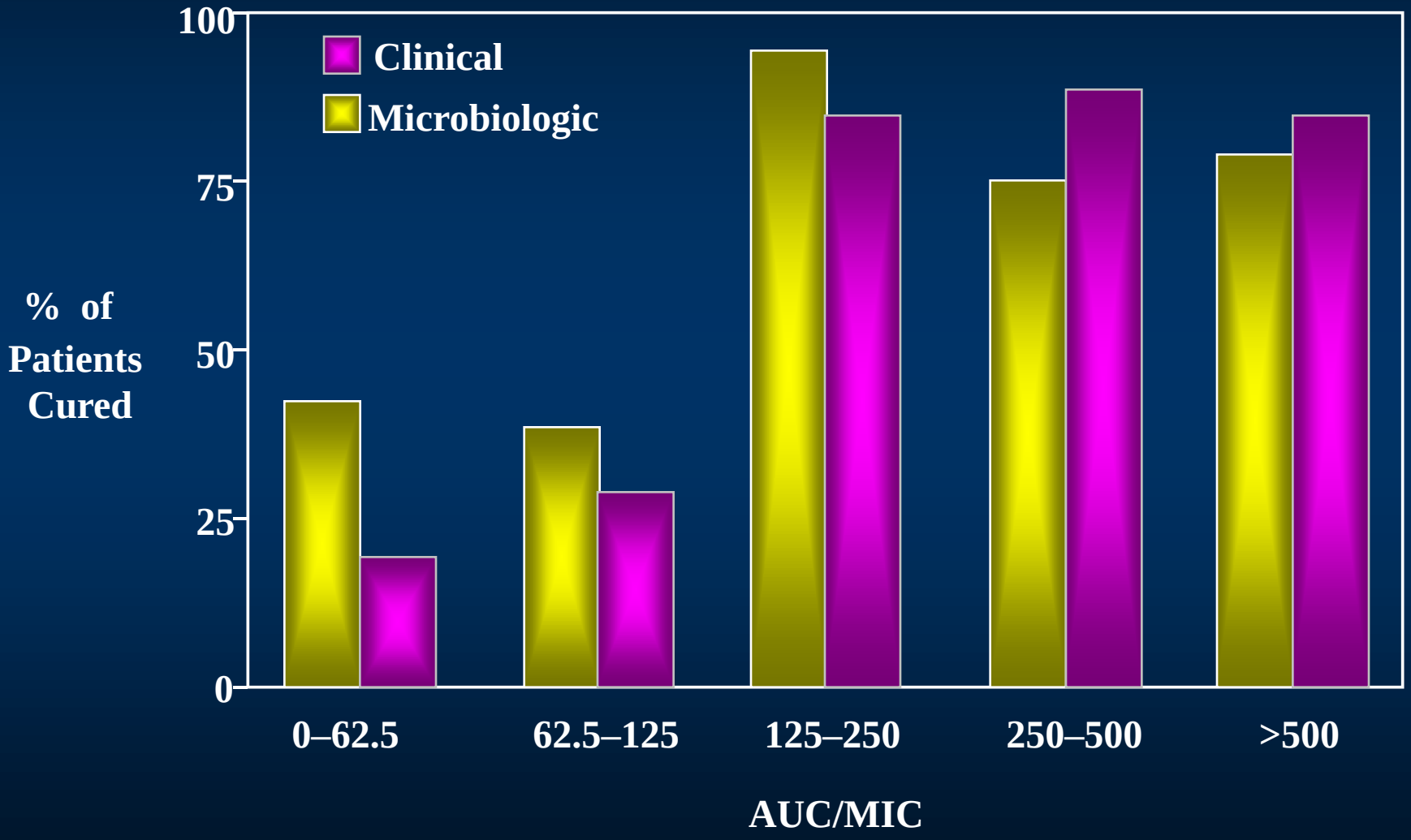
Successful response



Bulik, CC et. al. *Respiratory Medicine CME* In press

Fluoroquinolone: Human Data

Correlation Between AUC and Clinical Outcome



Forrest A et al Antimicrob Agents Chemother 1993; 37:1073

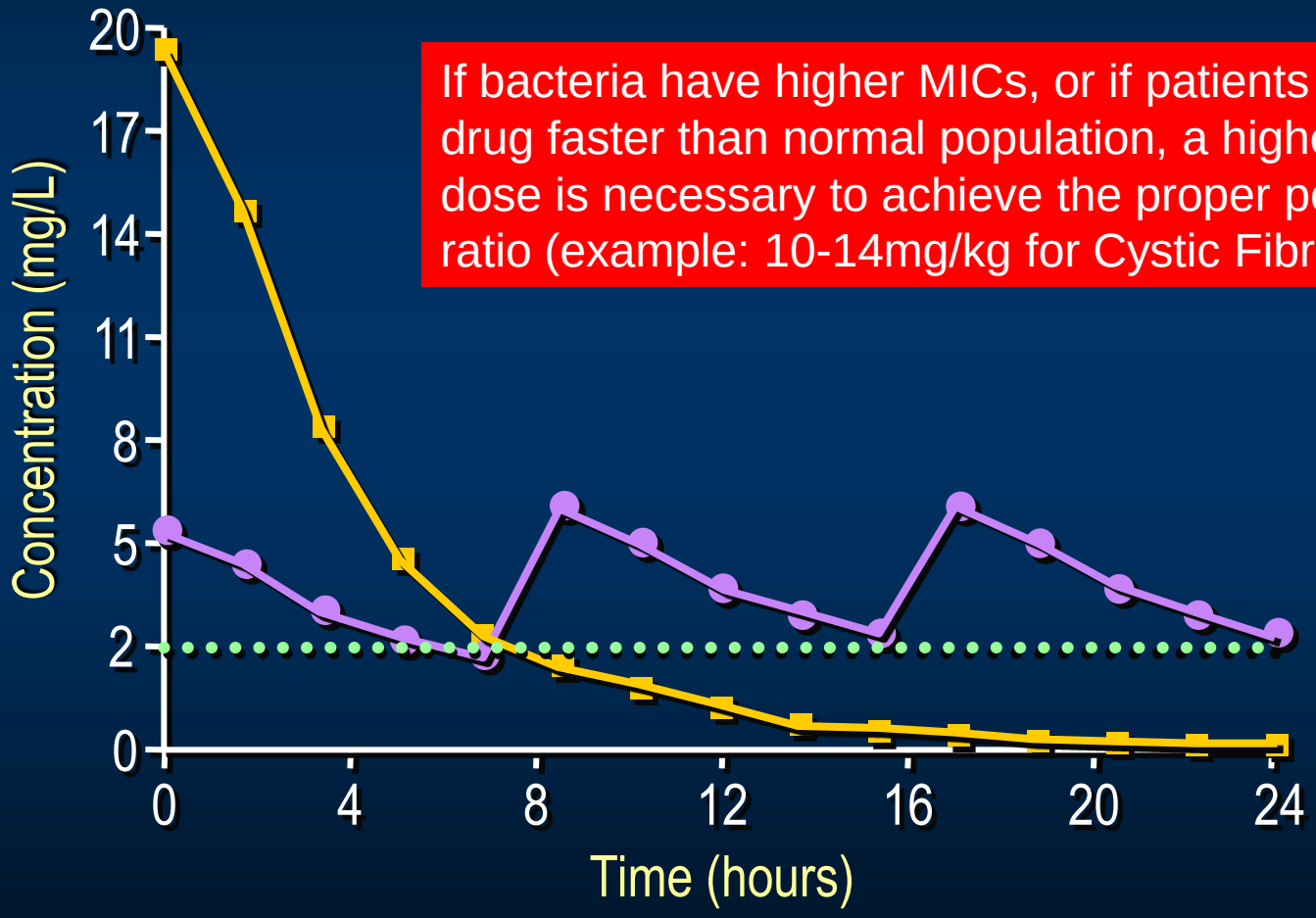
Fluoroquinolone Pharmacodynamics

- What's the problem?
  - What's your percentage of FQ-R PSA?
  - What's your percentage of FQ-R *E. coli*?
  - When original studies done, vast majority of organism MICs $\leq$ 0.5 μg/ml
    - Now majority of susceptible isolates just below the breakpoint
    - FQ doses don't optimize PD profile for many TARGET Gram Negative pathogens
      - Poor microbiologic eradication → promotes resistance
      - Collateral Damage → MRSA, *Clostridium difficile*

Vancomycin Pharmacodynamics

- Validity of MIC testing
- Applicability PKPD “targets”
  - AUC/MIC vs T>MIC
- Protein Binding

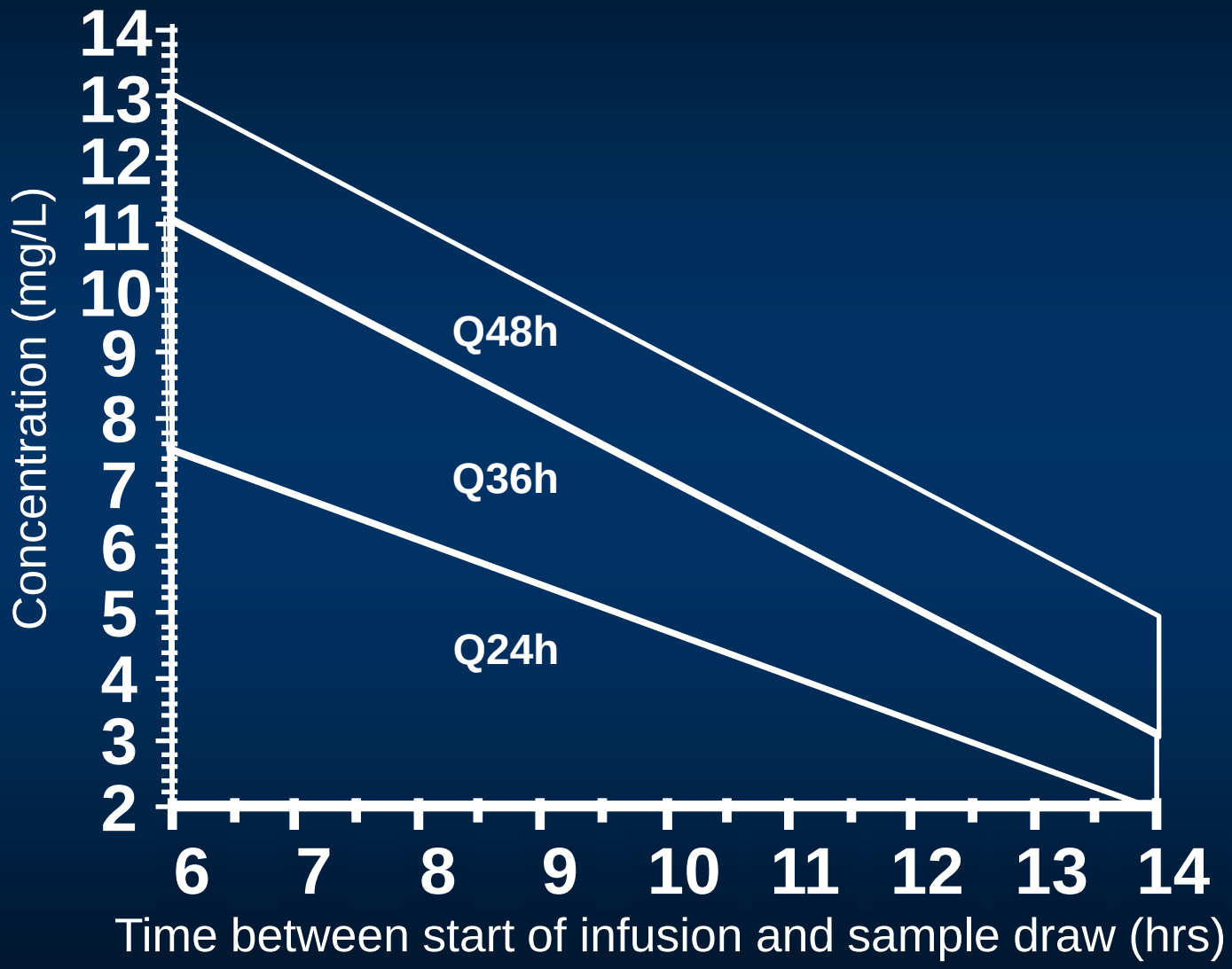
Once-daily vs. Conventional Three-times Daily Aminoglycoside Regimens



If bacteria have higher MICs, or if patients clear the drug faster than normal population, a higher mg/kg dose is necessary to achieve the proper peak/MIC ratio (example: 10-14mg/kg for Cystic Fibrosis patients

Nicolau DP et al. Antimicrob Agents Chemother 1995;39:650–655

Hartford Hospital ODA Nomogram



Nicolau DP et al. Antimicrob Agents Chemother 1995;39:650–655

Antibiotic Options Based on Phenotypic Resistance Profiles

Organism	Clinical Resistance Mechanism	First-Line Options	Other Considerations
Escherichia coli	ESBL producing	Imipenem or meropenem	Ertapenem, tigecycline, aminoglycosides, fluoroquinolones (only for urinary tract infections)
Klebsiella sp	AmpC producing	Cefepime	Imipenem, meropenem
	ESBL producing	Imipenem or meropenem	Ertapenem, tigecycline, aminoglycosides, fluoroquinolones (only for urinary tract infections)
	KPC producing	Tigecycline or polymyxins	Aminoglycosides, tetracyclines
Pseudomonas aeruginosa		Cefepime, meropenem, piperacillin-tazobactam, imipenem	Ceftazidime, aminoglycosides, fluoroquinolones (ciprofloxacin or levofloxacin)
	Carbapenamase producing	Polymyxins	Aminoglycosides, aztreonam (if a metallo-β-lactamase)
Acinetobacter baumannii		Imipenem or meropenem	Fluoroquinolones, doxycyclines, aminoglycosides, ampicillin-sulbactam
	Carbapenemase producing	Polymyxins	Tigecycline, aminoglycosides, ampicillin-sulbactam

ESBL = extended-spectrum β-lactamase.

Nicasio AM, et al. *Pharmacother* 2008;28:235-49

Problematic Gram-Negatives in the Hospital Setting and Mechanisms of Resistance

- *Pseudomonas aeruginosa*
  - AmpC production, efflux pumps (Mex*AB*-Opr*M*, etc), outer membrane porin changes (i.e., loss of Opr*D*), Metallo-Beta-Lactamase production (e.g., bla_{VIM}, bla_{IMP}), *gyrA*/*parC* mutations, aminoglycoside-modifying enzymes (AME), ESBL/KPC production (more recent)

- *Acinetobacter* species
  - AmpC, ESBL (TEM-1, SHV-type, CTX-M-type), and serine (bla_{OXA}) and metallo (bla_{VIM}, bla_{IMP}) carbapenemase production, outer membrane porin changes, AME, *gyrA*/*parC* mutations, efflux pumps

- Enterobacteriaceae (*Klebsiella* species, *E. coli*, *Enterobacter* species)
  - ESBL, Klebsiella-producing-carbapenemase (KPC-2, -3, -4, etc.) procuction, AmpC, outer membrane porin changes, plasmid mediated quinolone resistance gene (*qnrA*)

Bonomo RA, et al. *Clin Infect Dis* 2006;43:S49-56
Nicasio AM, et al. *Pharmacother* 2008;28:235-49

Trends in *Pseudomonas aeruginosa* Susceptibility in the USA

172 US Centers Participating in the TEST Surveillance Study

Antimicrobial	Percent Susceptible (%)		
	2005 (n=1428)	2006 (n=1325)	2007 (n=1054)
Amikacin	97.3	98.0	95.9
Cefepime	79.5	80.0	77.7
Ceftazidime	82.0	84.8	82.0
Imipenem	84.7	88.0	86.0
Levofloxacin	64.2	64.8	65.3
Pip/Tazo	90.8	92.1	90.2

MICs tested by MicroScan Panels or Sensititre plates at each participating institution

Dowzicky MJ, et al. Clin Ther 2008;30:2040-50.

Underdosing of levofloxacin selects for resistant mutants in wild type *P. aeruginosa*

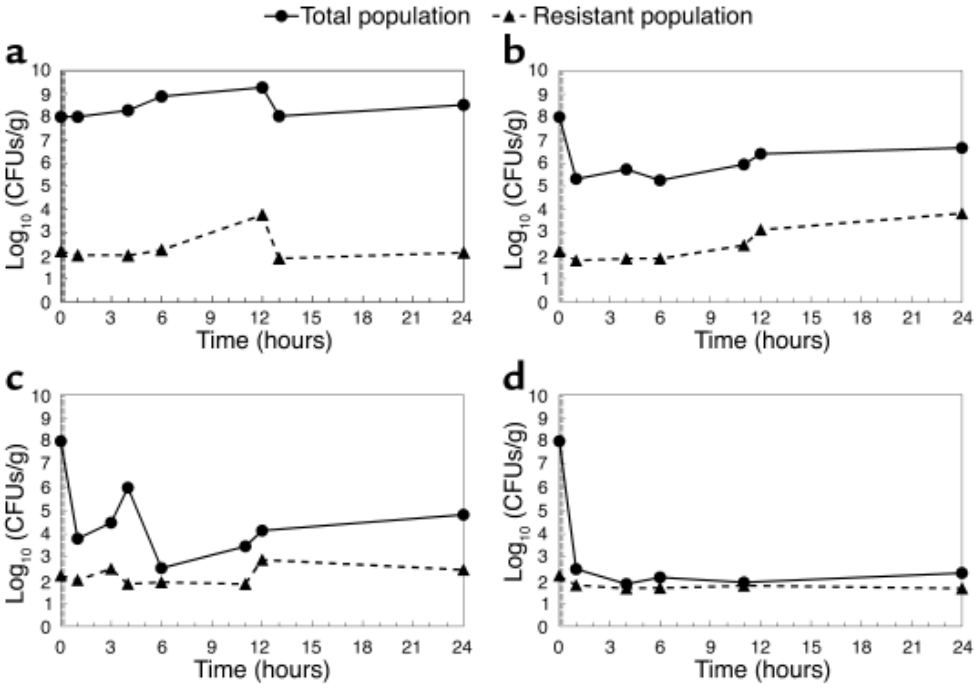
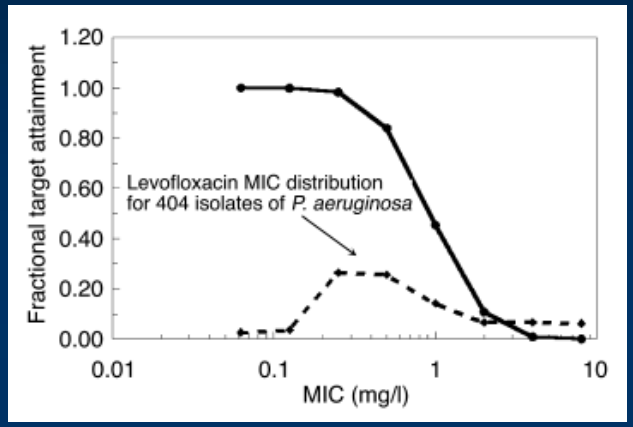


Figure 3
Effect of four drug doses on the total and resistant bacterial populations over 24 hours. Drug doses were 0, 90, 215, and 600 mg/kg (a–d, respectively). The 90-mg/kg dose allowed amplification of the resistant population by almost 2 $\log_{10}$ (CFUs/g). The 215-mg/kg dose allowed only minimal amplification of resistant mutants.

AUC/MIC ratios of 52 optimally selected out levofloxacin resistant mutants. The mechanism of this mutation was the overexpression of multiple efflux pumps, which appear to be present in the wild-type strain. An AUC/MIC of 157 was found to prevent the emergence of efflux mediated resistance.



The probability of levofloxacin 750mg once daily achieving an AUC/MIC of at least 157 against *P. aeruginosa*. Cumulative fraction of response was 61%.

Jumbe N et al. *J Clin Invest* 2003;112:275-85.

OPTAMA – US 2006

640 *E. coli*, 618 *Klebsiella* spp., 606 *P. aeruginosa* collected from ICU specimens of 15 centers in US

Table 3. Cumulative Fraction of Response (%) of Various Standard Infusion Dosing Regimens Against Three Gram-Negative Bacteria

		Escherichia coli	*Klebsiella* spp.	*Pseudomonas aeruginosa*	
Antibiotic	**Regimen**	***Pseudomonas***			2006
		2006			78.9
Cefepime	2g q8h – 3h infusion	97.8			90.0
					94.1
Ceftazidime	2g q8h – 3h infusion	96.3			96.7
					83.9
Imipenem	1g q8h – 3h infusion	88.6			ND
					91.9
Meropenem	1g q8h – 3h infusion	91.8			ND
					63.5
	2g q8h – 3h infusion	96.6			67.0
					ND
Piperacillin/ tazobactam	3.375g q8h – 4h infusion	81.3			74.6
					80.4
	4.5g q6h – 3h infusion	85.6			55.8
					83.8
					86.7
					92.6
					75.7
					79.1
					ND

MYSTIC = Meropenem Yearly Susceptibility Test Information Collection; ND = no data available.

Crandon JL, et al. *Ann Pharmacother* 2009;43:220-7

Cumulative Fraction of Response (CFR) Against *P. aeruginosa*

Antibiotic Regimen (infusion duration)	CFR (%)		
	MICU	SICU	NTICU
Cefepime			
2g q 12 hr (0.5 hr infusion)	46.5	50.0	86.4
2g q 8 hr (0.5 hr infusion)	58.8	60.8	96.8
2g q 8 hr (3 hr infusion)	61.2	63.6	98.7
Ciprofloxacin			
0.4g q 12 hr (1 hr infusion)	24.3	7.8	41.3
0.4g q 8 hr (1 hr infusion)	32.1	22.1	66.1
Meropenem			
0.5g q 6 hr (0.5 hr infusion)	49.0	44.5	89.1
2g q 8 hr (0.5 hr infusion)	58.5	53.6	91.5
2g q 8 hr (3 hr infusion)	69.1	58.4	92.1
Piperacillin/tazobactam			
4.5g q 6 hr (0.5 hr infusion)	55.5	43.3	85.0
4.5g q 6 hr (3 hr infusion)	60.7	50.2	91.7
18g q 24 hr (24 hr infusion)	60.7	50.3	91.7

Tobramycin 7mg/kg added

Pharmacokinetic (PK) parameters provided by published population PK studies

MICU = medical ICU; SICU = surgical ICU; NTICU = neurotrauma ICU

Nicasio AM, et al. *J Crit Care* 2010;25:69-77.

Order Set: MICU VAP Protocol B11I (H)

Order Items

	Must be ordered on all pts			
☑	VAP PROTOCOL (H) INITIATE - Protocol Coordinator - Joe Kuti, Pharm D 545-3612 or beeper 825-4336			
☑	RESPIRATORY CULTURE - Routine	T		
☑	CHEST AP SINGLE PORTABLE (RAD) -H	T		Routine - HHRad
☐	*** ATTENTION *** - Order 1st Line Regimen UNLESS patient 1. Is currently on Meropenem OR 2. Has had Meropenem in the last 14 days in which case order 2nd Line Regimen			
	1st Line Regimen Normal Renal			
☑	VANCOMYCIN DOSING BY PHARMACY - INITIATE - VAP Protocol			
☑	MEROPENEM IV -(H) - <ie Merrem > Administer 2 GM in SODIUM CHLORIDE 0.9% IV SOLN (H) 100 ML IV Q8H Infuse over 3 hours VAP Protocol Restricted to Infectious Disease Division or Cystic Fibrosis for pateints without VAP. Dosing is restricted to protocol.			
☑	TOBRAMYCIN DOSING BY PHARMACY - INITIATE - VAP Protocol			
☐	*** ATTENTION *** - 1st Line RENAL dose adjustments CrCL 30-49 Meropenem 500 mg IV Q6 CrCL < 30 Meropenm 500 mg IV Q8 CVVH - same dose as normal renal function Hemodialysis - Meropenem 500 mg IV Q12			
☐	MEROPENEM IV -(H) - <ie Merrem > MG in SODIUM CHLORIDE 0.9% IV SOLN (H) 50 ML IV Infuse over 30 minutes VAP Protocol Restricted to Infectious Disease Division or Cystic Fibrosis for pateints without VAP. Dosing is restricted to protocol.			
☐	TOBRAMYCIN DOSING BY PHARMACY - INITIATE - VAP Protocol - Renal Failure			

Outcomes

Measurement	Historic Control N=74	Clinical Pathway n = 94	P-value
Mortality, n (%)			
Infection-Related	16 (21.6)	8 (8.5)	0.029
28-Day	16 (21.6)	21 (22.3)	0.940
Crude	26 (35.1)	21 (28.7)	0.471
Appropriate Antibiotic Therapy, n (%)	36 (48.6)	53 (71.6)	0.007
Time to Appropriate Antibiotic, days			
Mean (SD)	1.73 (2.64)	0.76 (0.77)	0.065
Length of Stay, mean days (SD)			
Infection-Related	26.1 (18.5)	11.7 (8.1)	<0.001
ICU after VAP	24.6 (19.0)	20.2 (15.9)	0.128
Ventilator Duration after VAP	20.8 (16.6)	18.3 (15.7)	0.119
Total Hospital Length of Stay	43.3 (23.6)	37.9 (20.1)	0.113
Superinfections, n (%)			
All pathogens	26 (35.1)	15 (16.0)	0.007
MDR-pathogens	20 (27.0)	9 (9.6)	0.006

Infection-related mortality: death within 24 hours after completion of antibiotic therapy.

MDR: multidrug resistant

Nicasio AM, et al. *J Crit Care* 2010;25:69-77.

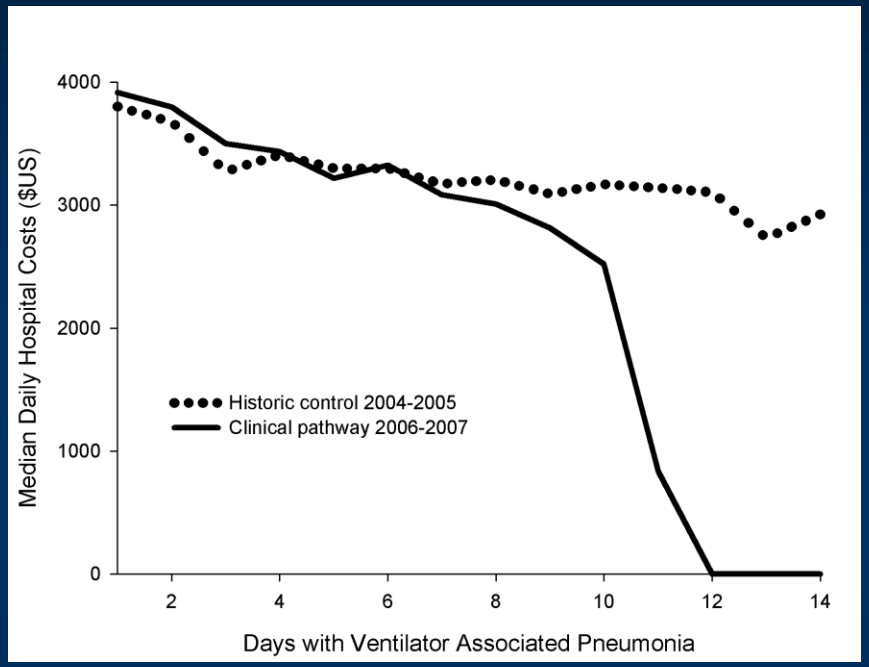
Outcomes in *P. aeruginosa* with Elevated Antibiotic MICs

Age/ Gender	ICU	APACHE II	Treatment(s)	MIC	Antibiotic Duration	Outcome
79 M	SICU	20	FEP 1g q12h; CIP 0.4g q24h	FEP: 16 μg/ml CIP: >32 μg/ml	3 days	Alive
78 M	SICU	24	FEP 2g q8h PI; TOB 420mg q24h	FEP: 16 μg/ml TOB: 3 μg/ml	8 days	Alive
61 M	MICU	14	MER 2g q8h PI; then FEP 2g q8h PI	MER: >32 μg/ml FEP: 4 μg/ml	8 days 8 days	Alive
20 F	NTICU	20	FEP 2g q8h PI; TOB 360mg q24h	FEP: 16 μg/ml TOB: 3 μg/ml	14 days	Alive
72 F	NTICU	22	FEP 1g q12h; TOB 480mg x1	FEP: 8 μg/ml TOB: 64 μg/ml	14 days	Died (not VAP attributed)
57 M	MICU	32	MER 2g q8h PI; TOB 480mg q24h	MER: 4 μg/ml TOB: 1.5 μg/ml	14 days	Alive
52 M	SICU	23	MER 2g q8h PI; TOB 425mg q24h	MER: 3 μg/ml TOB: 1.5 μg/ml	20 days	Alive
65 M	NTICU	21	FEP 2g q8h PI: TOB 500mg q24h	FEP: 4 μg/ml TOB: 1.5 μg/ml	4 days	Died (VAP attributed)
33 F	NTICU	22	FEP 2g q8h PI; TOB 380mg q24h; then MER 0.5g q6h	FEP: 8 μg/ml TOB: 1 μg/ml MER: 0.25 μg/ml	2 days 2 days 17 days	Alive

SICU: Surgical Intensive Care Unit; MICU: Medical ICU; NTICU: Neurotrauma ICU
FEP: cefepime; MER: meropenem; TOB: tobramycin, CIP: ciprofloxacin

Nicasio AM, et al. *J Crit Care* 2010;25:69-77.

Economics of the VAP Pathway



Variable	Control (n=73)	Pathway (n=93)	P-value
LOTVAP	27.1±18.5	12.7±8.1	<0.001
LOS	35.0±22.0	28.9±17.3	0.076*
COSTVAP	$75K	$35K	<0.001
COSTafter	$95K	$76K	0.077*
Antibiotic Cost	$934±1533	$766±755	0.45

Hospital costs similar for pathway ($24,501) and control ($28,817) over first week of VAP, but significantly lower for clinical pathway during week 2 ($12,231 vs $20,947, p<0.001).

* Treatment on Clinical Pathway was independently associated with lower total LOS after VAP (p=0.012) and lower total hospital costs after VAP (p=0.033) in multivariable models.

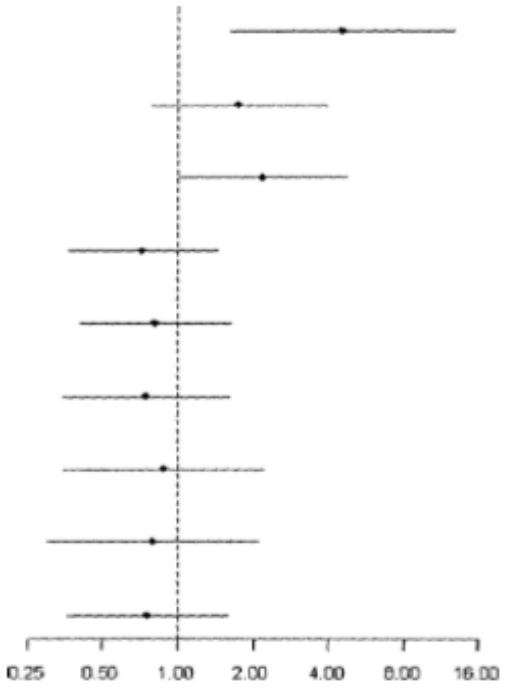
LOTVAP = length of VAP treatment; LOS = total length of hospital stay after identification of VAP; COSTVAP = hospital costs (2007$) of treating VAP; COSTafter = total hospital costs (2007$) of treating VAP after VAP identification; Antibiotic Cost = acquisition cost of antibiotics used to treat VAP

Nicasio AM, et al. *Pharmacother*. 2009 submitted.

Meropenem plus Ciprofloxacin versus Meropenem Monotherapy for VAP

Table 6. Subgroup analysis of patients with difficult-to-treat Gram-negative bacilli on enrollment (*Pseudomonas* species, *Acinetobacter* species, and other multidrug-resistant Gram-negative bacilli)

	Combination Therapy (n = 39)	Monotherapy (n = 17)	Combo/Mono RR (95% CI)[a]
Adequacy of empiric therapy, n (%)[b]	32 (84.2)	3 (18.8)	
Clinical resolution at 28 days, n (%)	20 (51.3)	5 (29.4)	
Microbiological resolution at 28 days, n (%)[c]	25 (64.1)	5 (29.4)	
Duration of mechanical ventilation[d]	10.7 (3.3, .)	15.0 (9.3, .)	
Duration of ICU stay[d]	14.2 (8.1, .)	21.2 (14.1, .)	
Duration of hospital stay[d]	55.0 (33.0, .)	111.4 (27.8, .)	
28-day mortality, n (%)	10 (25.6)	5 (29.4)	
ICU mortality, n (%)	9 (23.1)	5 (29.4)	
Hospital mortality, n (%)	13 (33.3)	7 (41.2)	



RR, relative risk; CI, confidence interval; ICU, intensive care unit.

[a]RR and 95% CI are adjusted for Acute Physiology and Chronic Health Evaluation II score and diagnostic technique by the stratified Mantel-Haenszel method for binary outcomes and the proportional hazards model for duration outcomes; [b]adequacy of therapy not available for one patient in each group, n = 38 for combination group, n = 16 for monotherapy group ($p < .001$); [c]$p = .014$; [d]median (interquarile range): The upper quartile range of the time to discharge is undefined for both groups because >25 of patients did not achieve the particular event.

Randomized controlled trial in 740 mechanically ventilated patients.

Heyland DK, et al. *Crit Care Med* 2008;36:737-44.

Combination Therapy for VAP caused by *Pseudomonas aeruginosa*

Empirical vs. Definitive

Table 4. Results of a Cox proportional hazard model showing unadjusted relations between recorded variables and the risk of death

	HR	95% CI	*p*
Age, yrs	1.03	1.01–1.04	<.0001
Male gender	1.02	0.60–1.72	.95
APACHE II score	1.01	0.98–1.03	.50
Type of patients			
Trauma	1.0 (referent)		
Surgical	3.42	1.49–7.86	.004
Medical	3.70	1.66–8.25	.001
Underlying diseases			
Hepatic cirrhosis	1.58	0.57–4.33	.37
Immunosuppression	1.32	0.60–2.87	.48
End-stage renal disease	1.2	0.41–2.97	.69
Chronic cardiac failure	3.33	1.88–5.89	<.0001
COPD	1.44	0.77–2.67	.24
Diabetes mellitus	1.51	0.95–2.5	.079
Alcoholism	1.47	0.82–2.63	.19
Smoking habit	0.95	0.58–1.63	.84
HIV infection	1.42	0.20–10.24	.73
Bacteremia	1.03	0.47–2.25	.94
Clinical presentation			
Sepsis	1.0 (referent)		
Severe sepsis	0.99	0.371–2.64	.98
Septic shock	2.47	0.98–6.19	.054
Recurrent VAP	0.41	0.1–1.67	.21
Prescribed empirical therapy			
Combination therapy	1.0 (referent)		
Monotherapy	1.56	1.00–2.48	.048
Effective empirical therapy			
Combination therapy	1.0 (referent)		
Monotherapy	1.08	0.60–1.94	.78
Inappropriate	2.65	1.58–2.42	<.0001
Definitive therapy			
Combination therapy	1.0 (referent)		
Monotherapy	0.94	0.51–1.75	.85

HR, hazard ratio; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; VAP, ventilator-associated pneumonia.

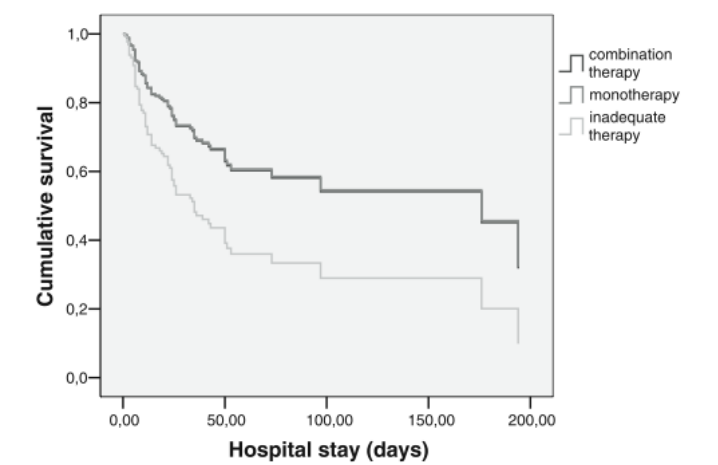


Figure 1. Cumulative survival curves of patients with inappropriate empirical antibiotic therapy compared with patients with effective monotherapy or effective combined therapy in the empirical therapy.

- Retrospective Multicenter Observational Cohort Study
- 187 episodes of monomicrobial PSA ventilator associated pneumonia
- Monotherapy was significantly associated with inappropriate therapy (90.5% vs 56.7%, p<0.001)

Garnacho-Montero J, et al. *Crit Care Med* 2007;35:1888-95.

Problematic Gram-Negatives in the Hospital Setting and Mechanisms of Resistance

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Bonomo RA, et al. *Clin Infect Dis* 2006;43:S49-56
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Antimicrobial	Percent Susceptible (%)		
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Cefepime	52.3	44.2	42.6
Ceftazidime	53.2	45.1	43.8
Imipenem	88.1	81.0	80.7*
Levofloxacin	54.2	44.2	42.2
Minocycline	89.3	87.7	80.7
Pip/Tazo	61.7	52.1	49.6

MICs tested by MicroScan Panels or Sensititre plates at each participating institution

* Meropenem tested in 2007.

Dowzicky MJ, et al. Clin Ther 2008;30:2040-50.

A. baumannii MIC distribution

Intravenous Antibiotic Pharmacodynamics against *Acinetobacter baumannii* from TRUST 12

- Benefits of Prolonged Infusion

349 *A. baumannii* from 56 US hospitals

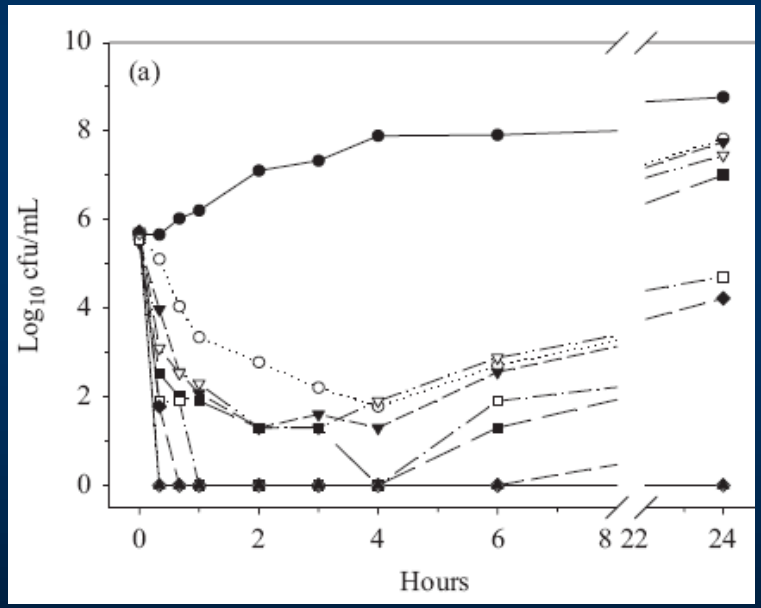
Antibiotic	Dosing Regimen	CFR (%) Standard Infusions (0.5 – 1 hour)	CFR (%) Prolonged Infusions (3 – 4 hours)
Cefepime	2g q12h	52.9	-
	2g q8h	60.9	64.0
Doripenem	0.5g q8h	60.3	67.5
	1g q8h	66.4	72.8
	2g q8h	73.7	80.6
Imipenem	1g q8h	66.8	71.6
Meropenem	1g q8h	64.4	68.9
	2g q8h	69.6	74.9
Pip/tazo	3.375g q8h	-	48.3
	4.5g q6h	48.1	52.6
Levofloxacin	750mg q24h	47.8	-

Koomanachai P, et al. *Clin Ther* 2010

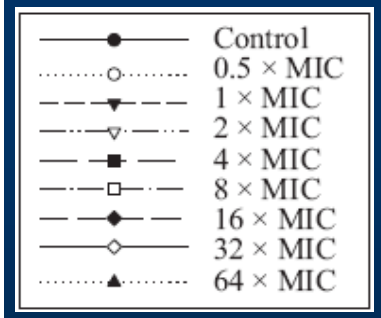
Colistin Pharmacodynamics against *Acinetobacter baumannii*: Potential Role for Combination Therapy

A Time-kill experiments with colistin sulphate at multiples of the MIC

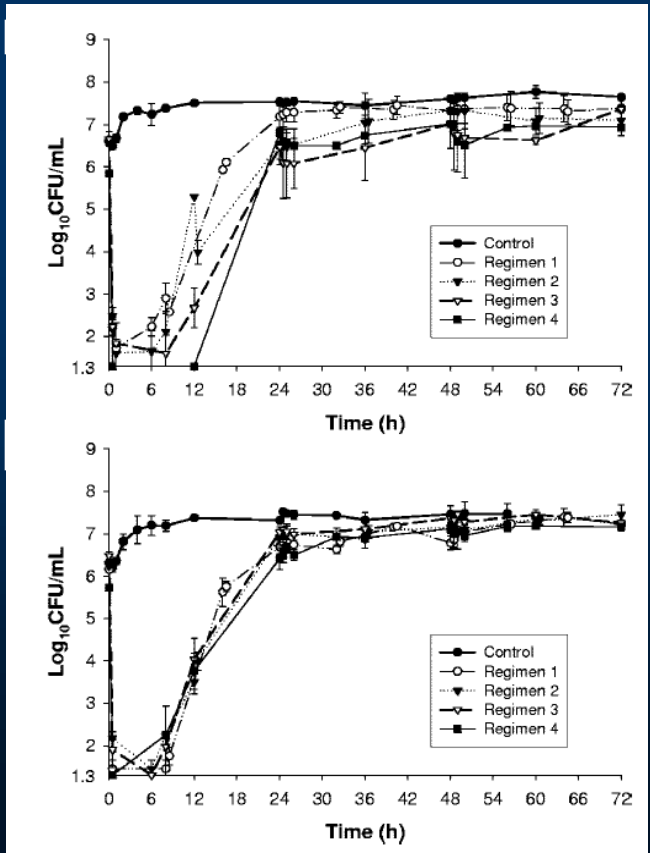
Concentration-dependent killing with no post-antibiotic effect



MIC = 2 mcg/ml



B In vitro pharmacodynamic model simulating colistin doses: 5mg/kg/d divided q8h, higher doses q12h and q24h, and continuous infusion (free drug concentration of 4.5 mcg/ml)



A: Owen RJ, et al. *J Antimicrob Chemother* 2007;59:473-7

B: Tan CH, et al. *Antimicrob Agents Chemother* 2007;51:3413-5

Colistin plus Rifampin for Treatment of Multidrug-Resistant *Acinetobacter baumannii* infections

29 critically ill patients with pneumonia (n=19) and bacteremia (n=10)

Colistin 2 million IU q8h (~10mg/kg/day) plus intravenous rifampin 10mg/kg q12h

Characteristic	No. (%), unless noted
APACHE II (mean ± SD)	17.03 ± 3.68
No. receiving mechanical ventilation	22 (75.8)
Duration of Treatment (mean ± SD)	17.7 ± 10.4 days
Length of Hospital Stay (mean ± SD)	33.2 ± 15.8 days
Clinical/Microbiological Response	22 (75.8)
30 day mortality	9 (31)
Nephrotoxicity	3 (10)

Bassetti M, et al. *J Antimicrob Chemother* 2008;61:417-20

Tigecycline Pharmacodynamics against *Acinetobacter baumannii* in a Murine Pneumonia Model

- Dose-fractionation studies to determine PK/PD parameter linked with tigecycline kill at 24 hours
- Five *A. baumannii* with tigecycline MICs 0.25-1 mcg/ml
- Free AUC/MIC was PD linked parameter
- *f*AUC/MIC to achieve 1- and 2-log CFU reductions was 2.17 and 8.78, respectively
- Translates into human doses of 200mg daily

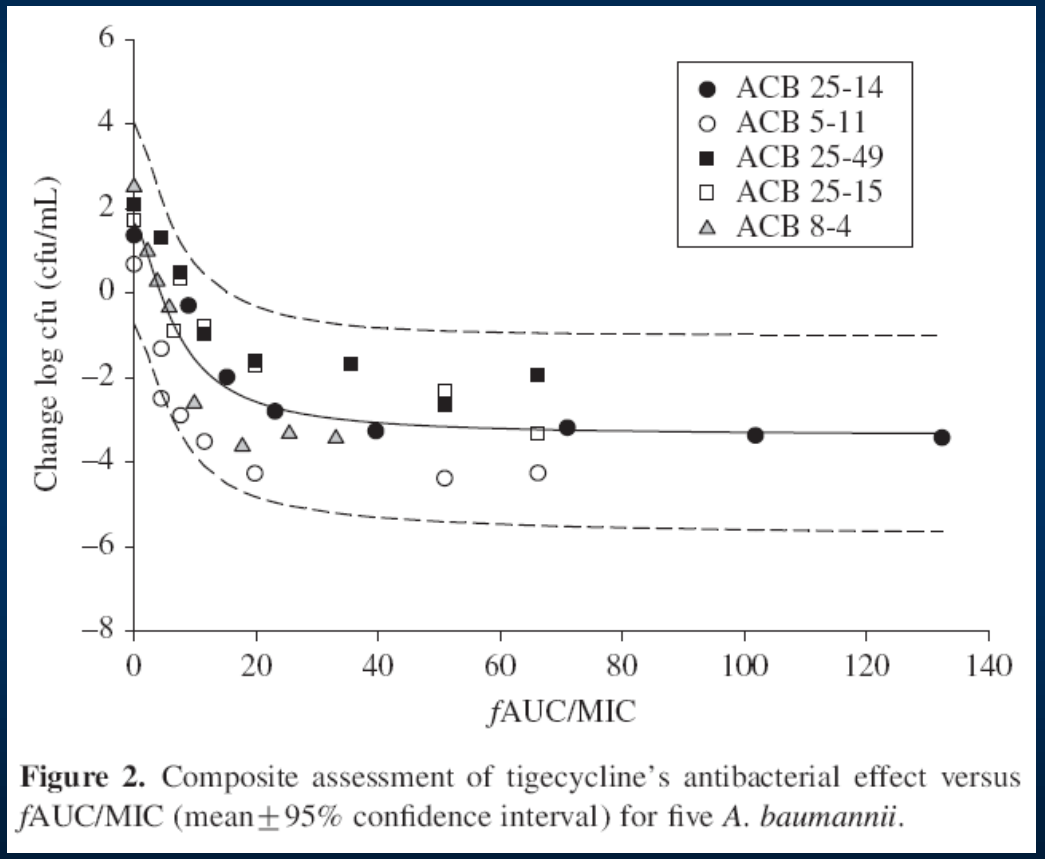
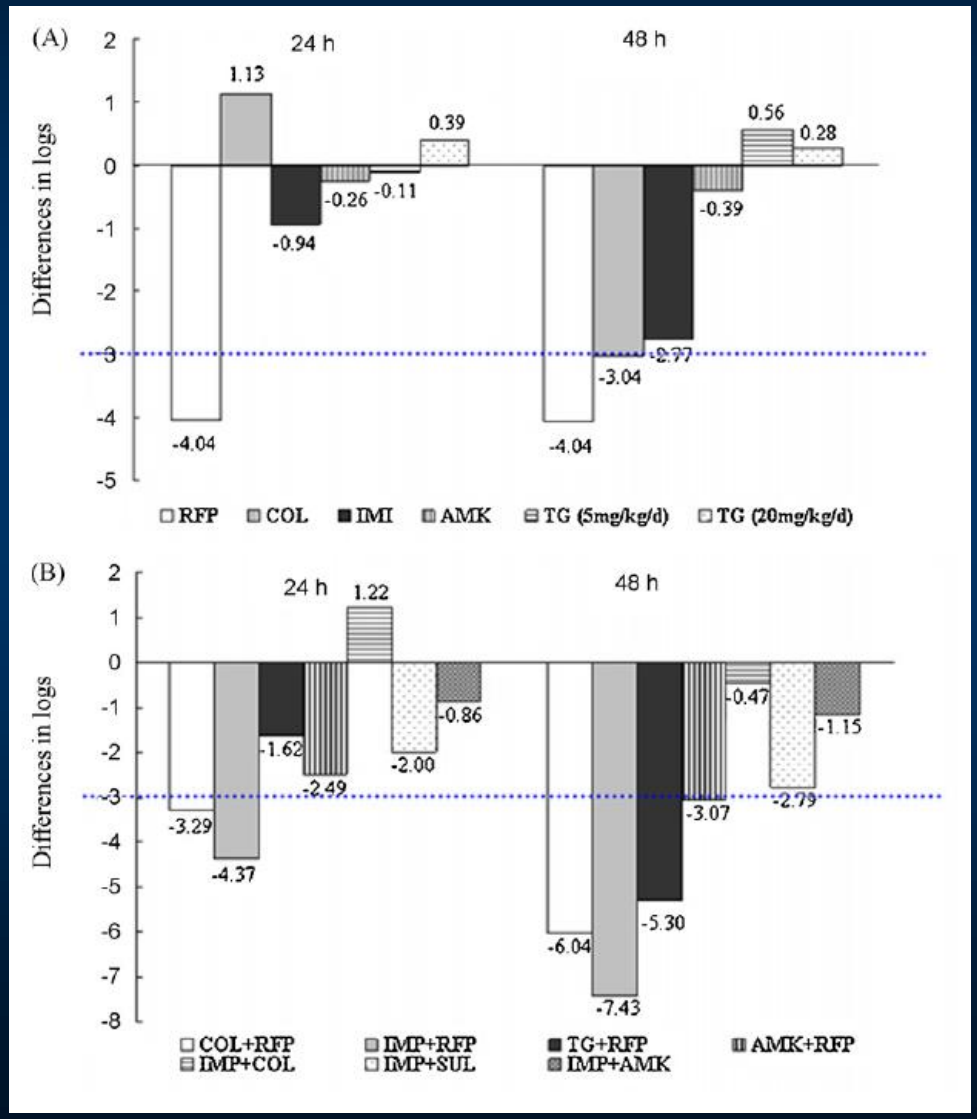


Figure 2. Composite assessment of tigecycline's antibacterial effect versus *f*AUC/MIC (mean ± 95% confidence interval) for five *A. baumannii*.

Koomanachai P, et al. *J Antimicrob Chemother* 2009;63:982-7

Monotherapy versus Combination Therapy for Carbapenem-resistant *Acinetobacter baumannii* Pneumonia in a Murine Infection Model

- Three *A. baumannii*:
  - bla_{OXA-51}, bla_{IMP-1}, bla_{VIM-2}
- Antibiotic dosages studied:
  - colistin 1.25 mg/kg q6h
  - imipenem 50 mg/kg q6h
  - sulbactam 30 mg/kg q6h
  - rifampicin 25 mg/kg q24h
  - tigecycline 5 mg/kg q24h
  - tigecycline 10 mg/kg q12h
  - amikacin 7.5 mg/kg q12h



Song JY, et al. *Int J Antimicrob Agents* 2009;33:33-9

High Dose Ampicillin/Sulbactam for Multidrug Resistant Acinetobacter baumannii VAP

BAL confirmed VAP: Colistin 3 MU q8h versus Amp/Sulb (2:1) 9 g q8h

	Colistin Group (n=15)	Amp/Sulb Group (n=13)	P-value
Clinical			NS
Success	9 (60)	9 (61.5)	
Improvement	2 (13.3)	1 (7.6)	
Failure	4 (26.6)	3 (23)	
Bacteriological			NS
Success	10 (66.6)	8 (61.5)	
Eradication	7 (46.6)	6 (46.1)	
28 day Mortality	5 (33.3)	3 (30.0)	NS
Nephrotoxicity	5 (33.3)	2 (15.3)	NS

Betrosian AP, et al. *J Infect* 2008;56:432-6.

Problematic Gram-Negatives in the Hospital Setting and Mechanisms of Resistance

- *Pseudomonas aeruginosa*
  - AmpC production, efflux pumps (Mex*AB*-Opr*M*, etc), outer membrane porin changes (i.e., loss of Opr*D*), Metallo-Beta-Lactamase production (e.g., bla_{VIM}, bla_{IMP}), *gyrA*/*parC* mutations, aminoglycoside-modifying enzymes (AME), ESBL/KPC production (more recent)

- *Acinetobacter* species
  - AmpC, ESBL (TEM-1, SHV-type, CTX-M-type), and serine (bla_{OXA}) and metallo (bla_{VIM}, bla_{IMP}) carbapenemase production, outer membrane porin changes, AME, *gyrA*/*parC* mutations, efflux pumps

- Enterobacteriaceae (*Klebsiella* species, *E. coli*, *Enterobacter* species)
  - ESBL, Klebsiella-producing-carbapenemase (KPC-2, -3, -4, etc.) procuction, AmpC, outer membrane porin changes, plasmid mediated quinolone resistance gene (*qnrA*)

Bonomo RA, et al. *Clin Infect Dis* 2006;43:S49-56
Nicasio AM, et al. *Pharmacother* 2008;28:235-49

KPC-2 (New York City) Susceptibility Results for 96 Isolates

Antibiotic	Susceptible	Intermediate	Resistant	MIC_{50}	MIC_{90}
Imipenem	0%	1%	99%	>32	>32
Meropenem	1%	0%	99%	>32	>32
Ertapenem	0%	0%	100%	>32	>32
Cefepime	40%	30%	30%	16	>32
Pip/Tazo	0%	1%	99%	>128	>128
Amikacin	45%	52%	3%	32	32
Ciprofloxacin	2%	0%	98%	>8	>8
Doxycycline	66%	10%	24%	4	>32
Tigecycline	100%	0%	0%	0.5	1
Polymyxin B	91%	-	9%	2	2

Bratu S, et al. *J Antimicrob Agents* 2005;56:128-32.

Carbapenems for KPCs - Single Center Experience

Characteristics of inpatients with treated KPC *K. pneumoniae* infections

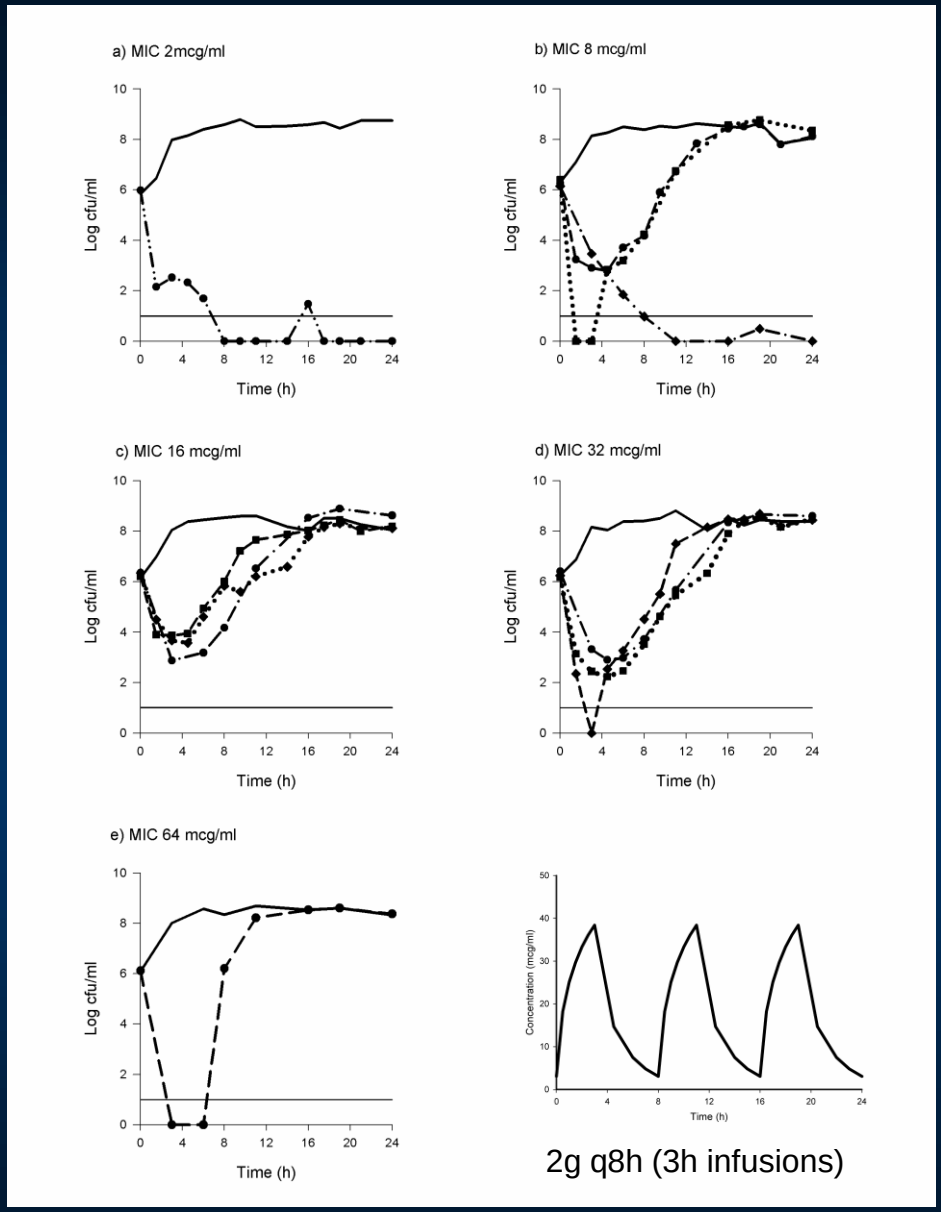
Age (year)/sex	Underlying condition	Acute illness (tested isolate site)	Apache II	MIC (Vitek/Etest)	Treatment (days)	Response
46/F	Skin graft	Bacteremia (blood)	6	4/8	Imipenem (7), port removal	Microbiologic and clinical success
61/F	CHF	Pyelonephritis			Imipenem (7)	Microbiologic and clinical success
82/M	None	Urosepsis (blo			Imipenem (14)	Microbiologic and clinical success
92/M	Dementia	Pneumonia (re			Imipenem (3)	Clinical success
64/F	Esophageal cancer	Tracheobronch			Imipenem (12)	Microbiologic failure
76/M	Cerebral hemorrhage	Tracheobronch			Meropenem (7)	Clinical and microbiologic failure
69/F	Metastatic cancer	Pneumonia (re			Imipenem (6)	Clinical failure/death
77/M	MRSA 1 abscess	Tracheobronch			Imipenem (7)	Microbiologic failure
52/M	Melanoma	UTI (urine)			Imipenem (14)	Microbiologic failure
67/M	Polyneuropathy	Urosepsis (blo			Tigecycline (7)	Clinical and microbiologic failure
65/M	Lung mass	Tracheobronchitis (resp)	15	4/1	Tigecycline (7)	Clinical and microbiologic success
83/F	Laryngeal cancer	Pneumonia (blood)	14	≥16/≥32	Tigecycline (7)	Clinical success
39/F	Stem cell transplant	Urosepsis (urine)	12	8/8	Tigecycline (14)	Clinical success
79/M	None	Pneumonia (resp)	27	8/32	Tigecycline (14)	Clinical success
19/M	Trauma, craniotomy	Shunt associated meningitis (CSF)	28	N/A	Tigecycline/gentamicin[a]	Clinical and microbiologic success
79/F	s/p CABG	Bacteremia (blood)	29	8/2	Tigecycline/imipenem	Clinical failure/death
0/M	Seizures	Pneumonia (resp)	n/a	≥16/≥32	Gentamicin (7)	Clinical success
60/F	Metastatic cancer	Wound (wound)	25	8/≥32	Amikacin (7)	Clinical success
59/F	ESRD	Line infection (blood)	22	≥16/≥32	Gentamicin (10)	Clinical and microbiologic success
60/F	Pelvic infection	Bacteremia (blood)	24	≥16/8	Meropenem (10)	Clinical and microbiologic failure
50/M	Liver transplant	Bacteremia	9	≥16/8	Meropenem (7)	Clinical and microbiologic success

4/9 (44%) success rate for organisms defined as susceptible

Weisenberg SA, et al. *Diagn Microbiol Infect Dis* 2009;64:233-5.

High Dose, Prolonged Infusion Meropenem against KPCs in an In Vitro Pharmacodynamic Model

Isolate	MIC	Targeted fT>MIC (%)	Achieved fT>MIC for each dosing interval (%)		
			0-8	8-16	16-24
KPC378	2	100	100	100	100
KPC328	8	69	69	72	78
KPC351	8	69	69	62	50
KPC354	8	69	68	56	3
KPC353	16	47	38	59	0
KPC357	16	47	12	0	0
KPC360	16	47	0	0	0
KPC334	32	16	0	0	0
KPC368	32	16	0	0	0
KPC375	32	16	0	0	0
KPC361	64	0	0	0	0



Bulik CA, et al. 49th ICAAC 2009 – Abstract #A-019

Summary

- Few novel antibiotics in the pipeline for treatment of emerging multi-drug resistant bacteria
- Pharmacodynamic concepts, along with knowledge of the antibiotic MIC, may permit dosage optimization and successful treatment of certain resistant organims, particularly for beta lacatms and aminoglycosides
- Combination therapy has a potential role in treatment of some MDR Gram-negatives, particularly *Acinetobacter baumannii*
- Mechanisms of resistance may effect the pharmacodynamics of ‘optimized’ dosing regimens