Translating PK/PD Concepts into Dosing Strategies

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PK/PD Indices for Various Antimicrobials

T>MIC	Peak/MIC or AUC/MIC	AUC/MIC
Penicillins	Aminoglycosides	Azithromycin
Cephalosporins	Fluoroquinolones	Macrolides
Carbapenems	Daptomycin	Clindamycin
Aztreonam	Polymyxins	Tetracyclines
Fosfomycin		Tigecycline
		Linezolid
		Vancomycin
		TMP/SMZ

"PK-PD of antimicrobial therapy: It's not just for mice anymore"

Disease	Drug	Human Value	Mice Value
HAP	Quinolones	AUC/MIC 62-75	AUC/MIC 70-90
	Ceftazidime	T>MIC 45%	T>MIC 43%
CAP	Quinolones	AUC/MIC 34	AUC/MIC 35
	ß-Lactams	T>MIC 40%	T>MIC 30-45%
SSTI	Linezolid	AUC/MIC 110	AUC/MIC 83
	Tigecycline	AUC/MIC 18	AUC/MIC 15-20
CB-MRSA	Vancomycin	AUC/MIC 400	AUC/MIC 399

Ambrose et al Clin Infect Dis 2007;44:79; Muller AE, et al. J Antimicrob Chemother. 2013;68:900; Lee DG, et al. Antimicrob Agents Chemother. 2013;57:1434

Optimizing Antimicrobial Dosing

Time-dependent killing and minimal or no persistent effects

Seen with all beta-lactams and fosfomycin

Time above MIC is major PK/PD indice correlating with efficacy

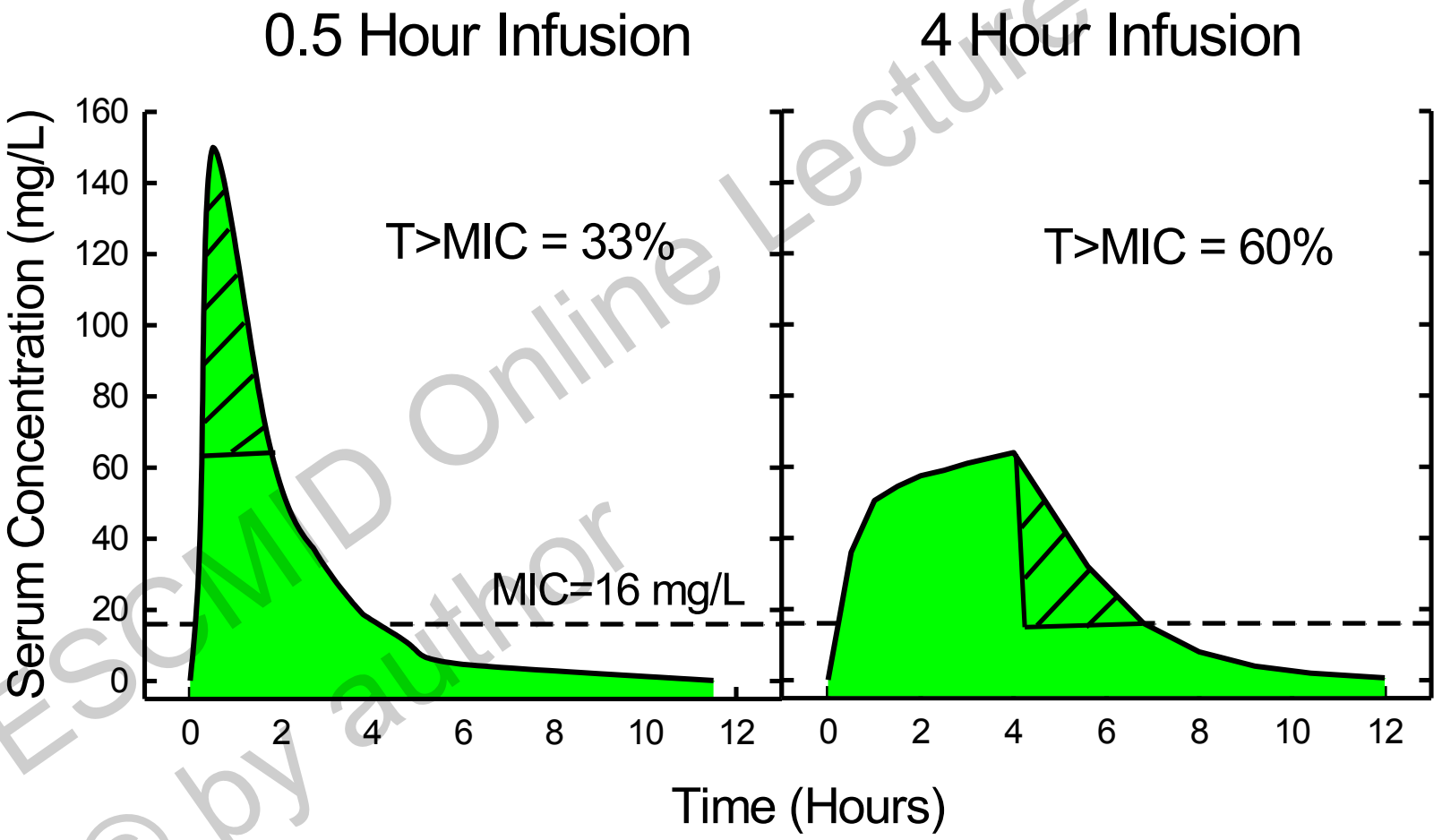
Goal of optimal dosing regimen: enhance duration of exposure; maximum killing occurs when levels are constantly above 4-5 times MIC

DALI (Defining Antibiotic Levels in Intensive Care Unit Patients

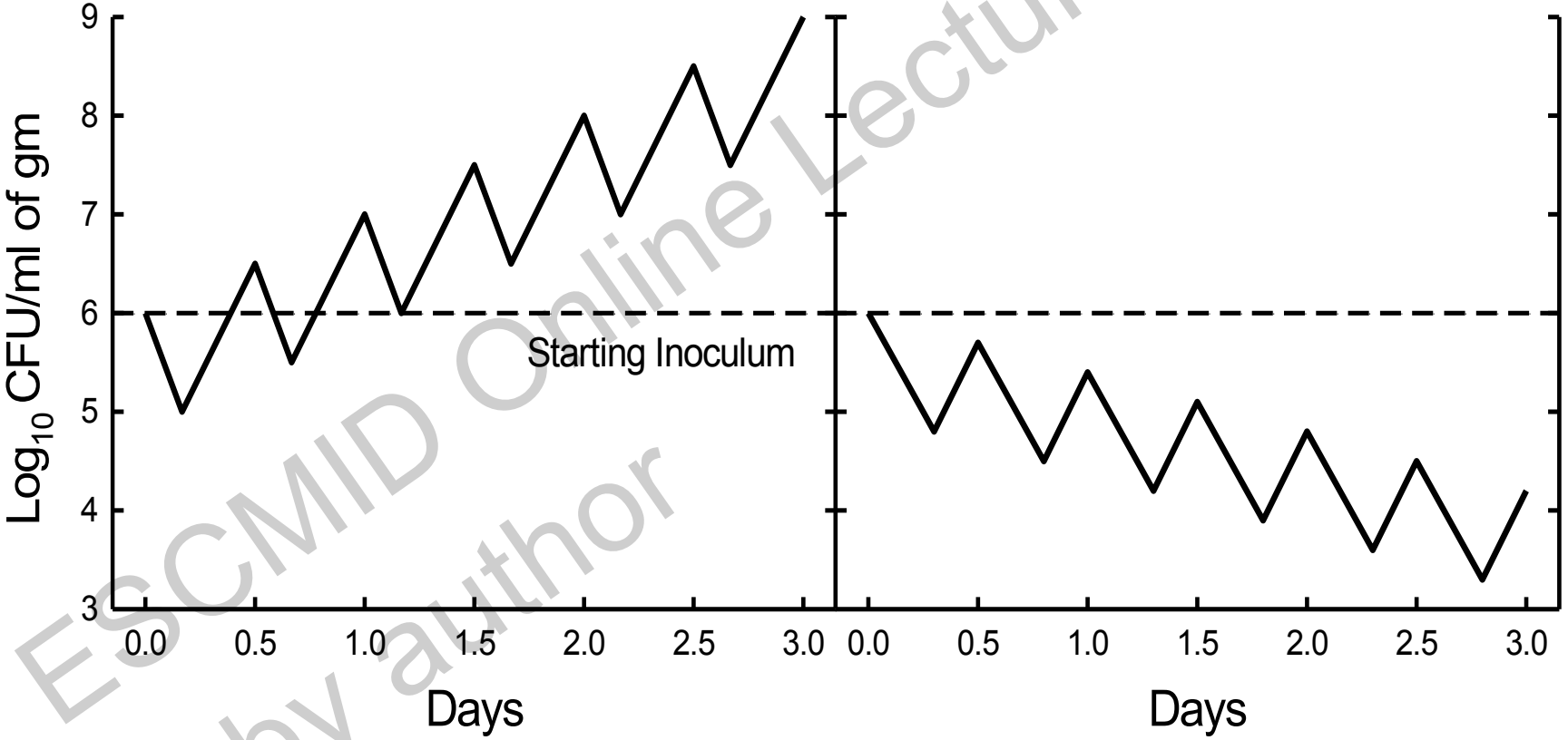
- Prospective, multinational pharmacokinetic study involving 384 patients correlating outcome with free drug T>MIC for 8 β-lactams at 50% and 100% of dosing interval
- Of 248 patients treated for infection, 18% did not achieve 50% *f*T>MIC and were 32% less likely to have a clinical cure (OR 0.68; p<0.009)
- Positive clinical outcome was also associated with increasing concentration/MIC ratios at 50% and 100% of dosing interval
- Weakness: Effect of concomitant antibiotics not assessed, and only 25% of patients' pathogens had an exact MICs

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

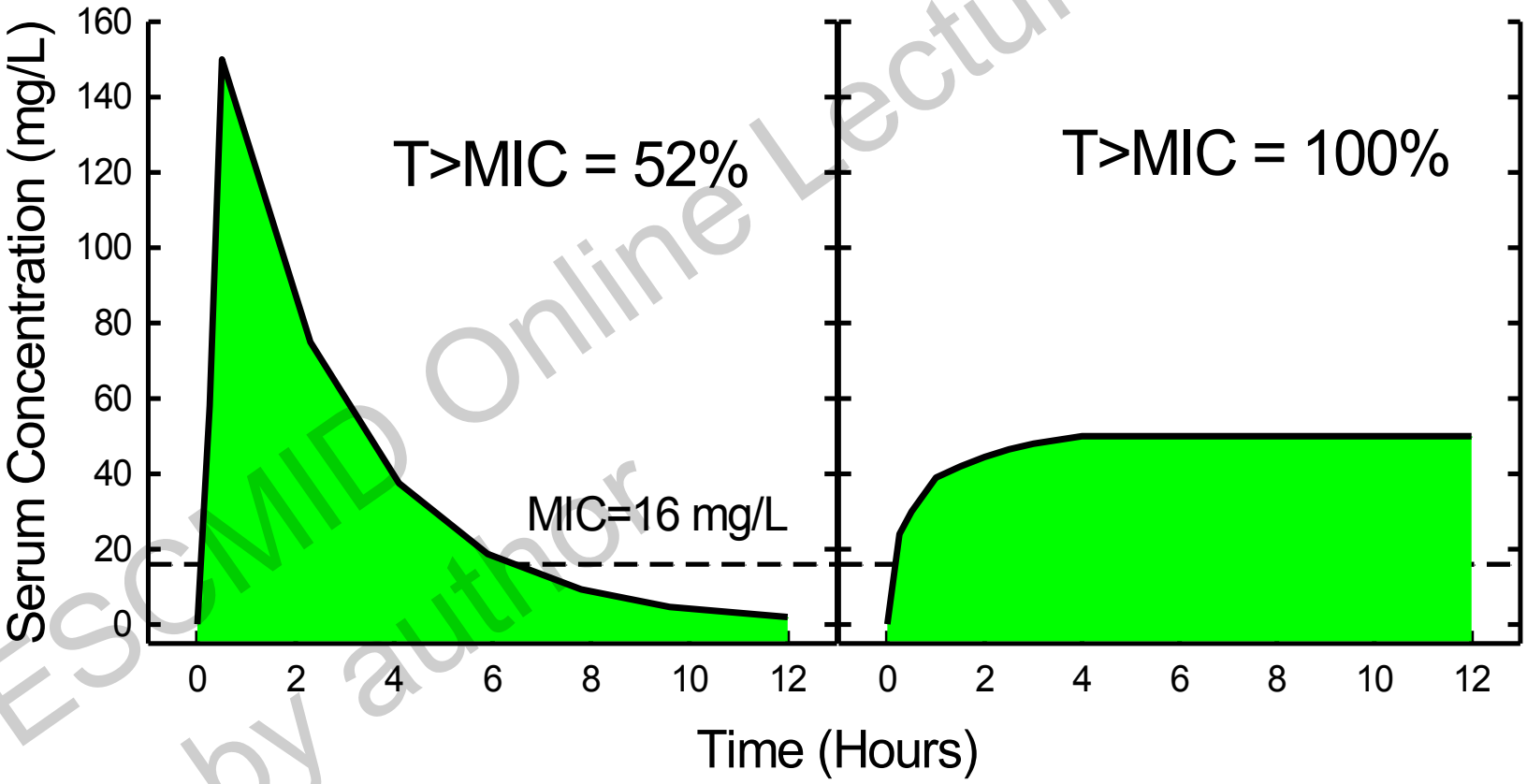
T>MIC for 30 minute and 4-hr Infusions of a β-Lactam Antibiotic



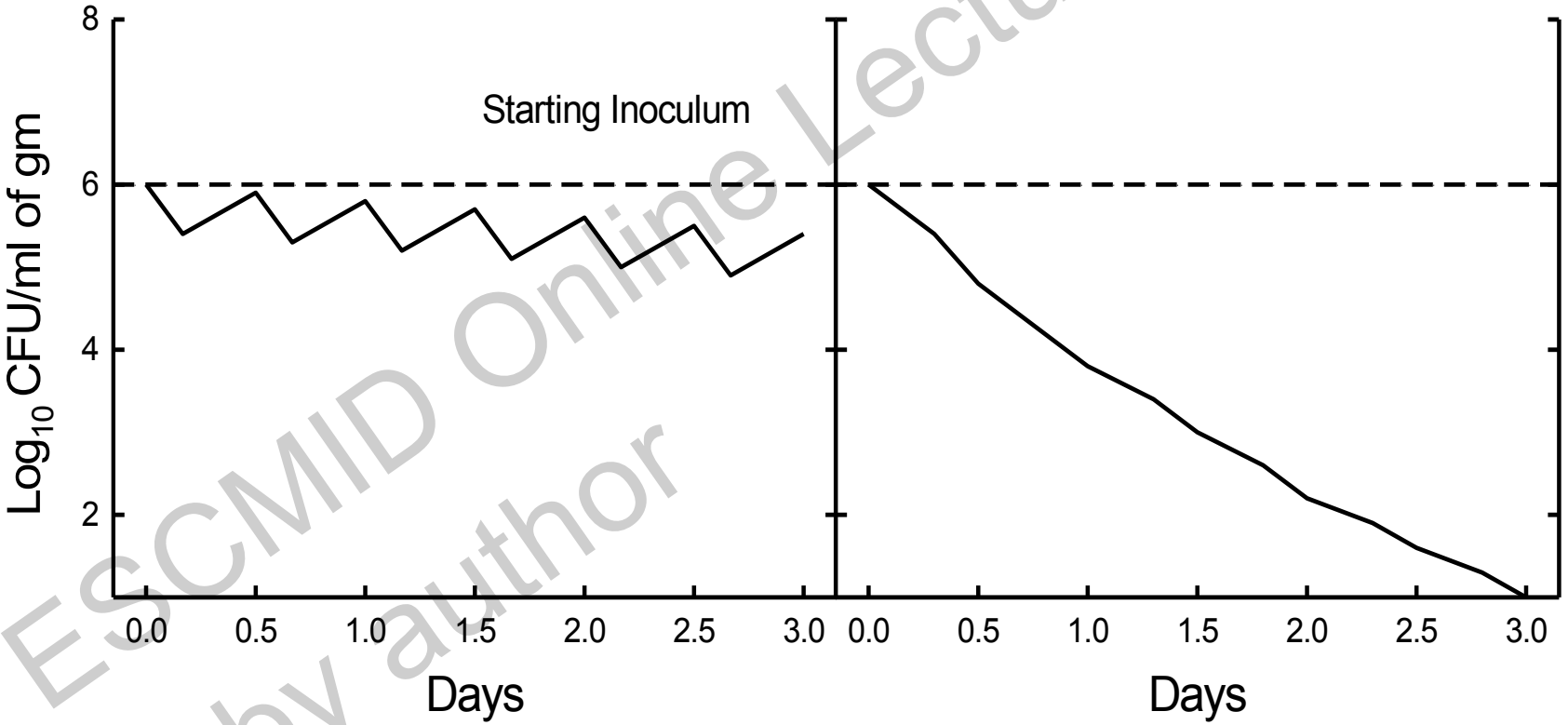
Time Course of Antimicrobial Activity for 30-min and 4-hr β-Lactam Infusions



T>MIC for 30 minute and Continuous Infusions of a β-Lactam Antibiotic



Time Course of Antimicrobial Activity for 30-min and Continuous β-Lactam Infusions



Primary and Secondary Endpoints in Clinical Trials

Usual Parameters

- All-cause mortality
- 14 and 30-day mortality
- Clinical cure
- Microbiological cure
- Infection recurrence by 14 days after therapy
- Super-Infection
- Adverse events
- Serious adverse events

Rate of Improvement

- Duration of ICU stay
- Ventilator free days
- Pressor free days
- Duration of hospital stay
- Duration of bacteremia
- Total drug used
- Rate of improvement in inflammatory markers
- ICU costs
- Total hospital costs

Meta-Analysis and Systematic Review of Continuous vs Intermittent Bolus Antibiotic Infusions

- 29 open-label or blinded parrallel-group randomized clinical trials involving over 1600 patients
- No difference in all-cause mortality (RR 0.89; CI:0.67-1.20)
- No difference in clinical cure (RR 1.00; CI:0.93-1.08)
- No difference in recurrences (RR 1.08; CI:0.60-1.94)
- No difference in adverse effects (RR 1.02; CI 0.94-1.12)

Shiu J, et al. Cochrane Database Syst Rev 2013; 3:CD008481

Meta-Analysis and Systematic Review of Prolonged vs Intermittent Bolus β-Lactam Infusions

- 29 studies (18 randomized controlled trials and 11 observational studies) involving 2206 patients
- Prolonged infusion reduced mortality (RR 0.66; CI:0.53-0.83) and improved clinical cure (RR 1.34; CI:1.02-1.76).
- However, no significant reduction in mortality or improvement in clinical cure in randomized studies

Teo J, et al. Int J Antimicrob Agents 2014; Epub

Some Documented Benefits of Continuous/Prolonged Infusion of β-Lactam Antibiotics

Continuous/prolonged infusion vs short intermittent dosing

- Much lower total dosage of antibiotic
  (Korbita IP et al. Expert Rev Anti Infect Ther. 2013; 11:585)
- Shorter ICU stay (8 days vs 18.5 days; p=0.04)
  (Bauer KA et al. Antimicrob Agents Chemother. 2013: 57; 2907)
- Shorter hospital stay (21 vs 38 days; p=0.02)
  Lodise TP Jr et al. Clin Infect Dis. 2007; 44:357)
- Lower costs ($23,000 less per patient)
  (Bauer KA et al. Antimicrob Agents Chemother. 2013: 57; 2907)

Optimizing Antimicrobial Dosing

Concentration-dependent killing and prolonged persistent effects

Seen with aminoglycosides, daptomycin, polymyxins, fluoroquinolones

AUC/MIC and Peak/MIC are major PK/PD indices correlating with efficacy

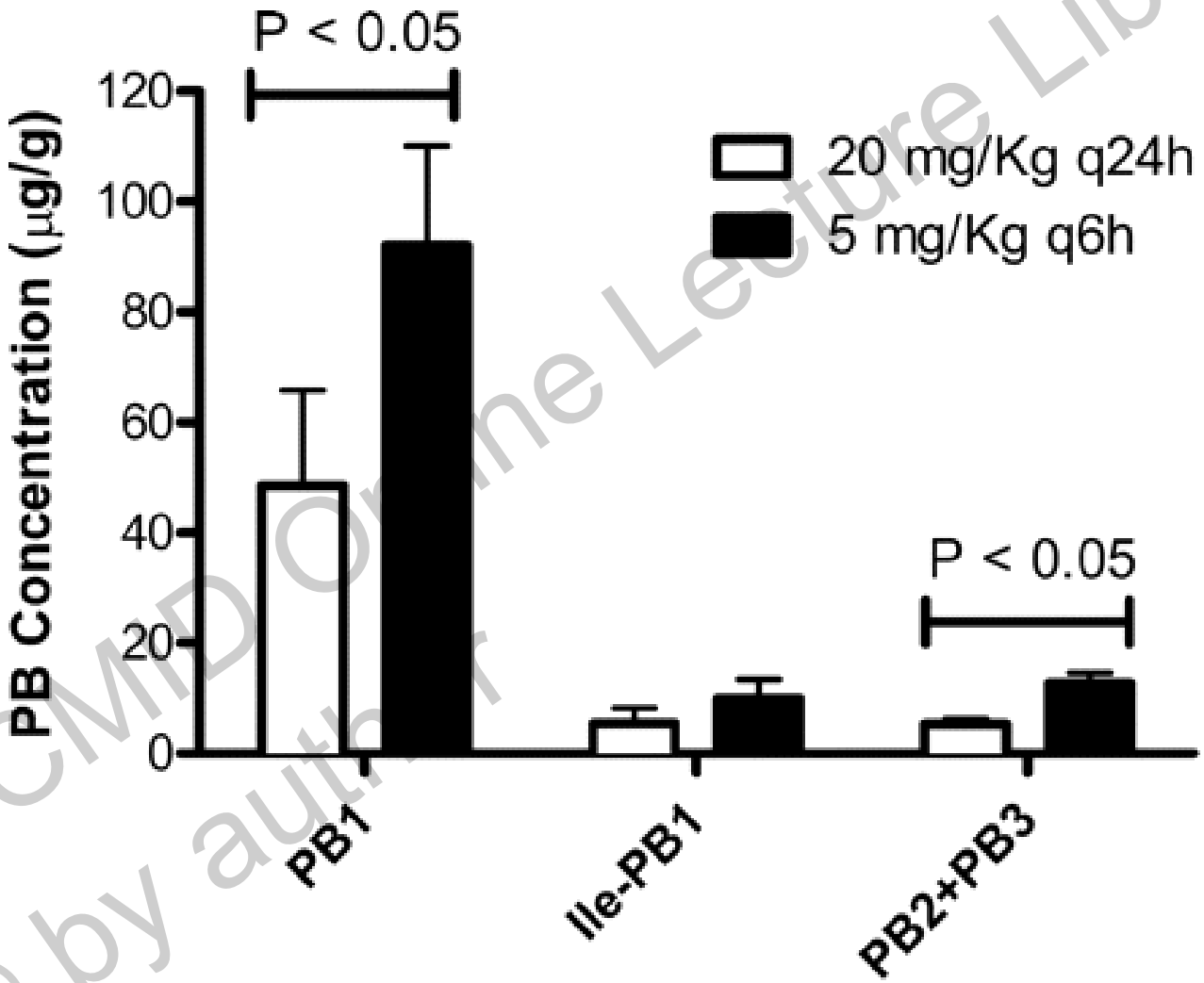
Goal of optimal dosing regimen: maximize both peak concentrations and AUC

Aminoglycoside (and Polymyxin) Nephrotoxicity

- Megalin is a lipoprotein on the brush border of renal tubular cells that binds aminoglycosides and polymyxins and is important for uptake of these drugs by pinocytosis
- Binding to megalin by aminoglycosides and polymyxins is saturable
- Once-daily dosing of aminoglycosides results in less early uptake in human kidneys than thrice-daily; nephrotoxicity occurs later with once-daily dosing – usually after 5-7 days
- Once-daily dosing of polymyxin results in less uptake in rat kidney

Nagai & Takano Drug Metab Pharmacokin 2004;19:159
Rougier F et al Antimicrob Agents Chemother 2003; 47:1010
Phe K et al. Antimicrob Agents Chemother 2014;58:Epub

Concentrations of Major Polymyxin Components in Rat Kidney



Phe K, et al Antimicrob Agents Chemother 2014; 58 Epub

Optimizing Use of Aminoglycosides

- Once daily treatment of 5-10 mg/kg (gentamicin, tobramycin) or 15-30 mg/kg (amikacin) for short periods (5-7 days)

- For non-urinary tract infections: Target attainment inadequate for monotherapy against organisms with MICs > 0.5 mg/L (gentamicin, tobramycin) or > 2.0 mg/L (amikacin)

- Addition of aminoglycoside to ß-lactam increases initial appropriate antibiotic therapy for resistant organisms, reduces early mortality in septic shock and increases ventilator/pressor-free days in ICU

Risk of Renal Toxicity with Short-Term (≤ 5 Days) Gentamicin Therapy

- All patients had community-acquired bacteremia

Short-Term Gentamicin	Rise in Serum Creatinine	Mortality
Yes	13/165 (7.9%)	7.9%
No	13/150 (8.7%)	7.3%

- Renal impairment in bacteremic patients is independent of short-term gentamicin therapy

Spanggard et al Scand J Infect Dis 2011; 43:953.

Daptomycin Myopathy and CPK Rise

- Study in dogs showed once-daily administration of daptomycin resulted in less myopathy than the same daily dose of drug divided into three 8-hr doses
- Human studies with once-daily dosing identified that a daptomycin trough (Cmin) value of ≥ 24.3 mg/L has an increased probability for CPK rise.
- Higher doses of daptomycin have been suggested to achieve AUC_{0-24}/MIC ≥ 666 in critically ill patients.

Daily Dose	AUC_{0-24}/MIC ≥ 666	Cmin ≥ 23.4 mg/L
6 mg/kg/day	82.1%	0.08%
8 mg/kg/day	91.3%	0.78%
10 mg/kg/day	95.4%	2.64%

Oleson FB Jr, et al. Antimicrob Agents Chemother 2000; 44:2948; Bhavnani SM et al Clin Infect Dis 2010; 50:1568; Falcone et al. Clin Infect Dis 2013; 57:1568

Optimizing Antimicrobial Dosing

Time-dependent killing and moderate to prolonged persistent effects

Seen with macrolides, azithromycin, tetracyclines, clindamycin, linezolid, and glycopeptides

AUC/MIC is major PK/PD indice correlating with efficacy

Goal of dosing regimen: optimize amount of drug; maximum killing when T>MIC 100%

24-Hr AUC/MIC Values and Efficacy for Vancomycin

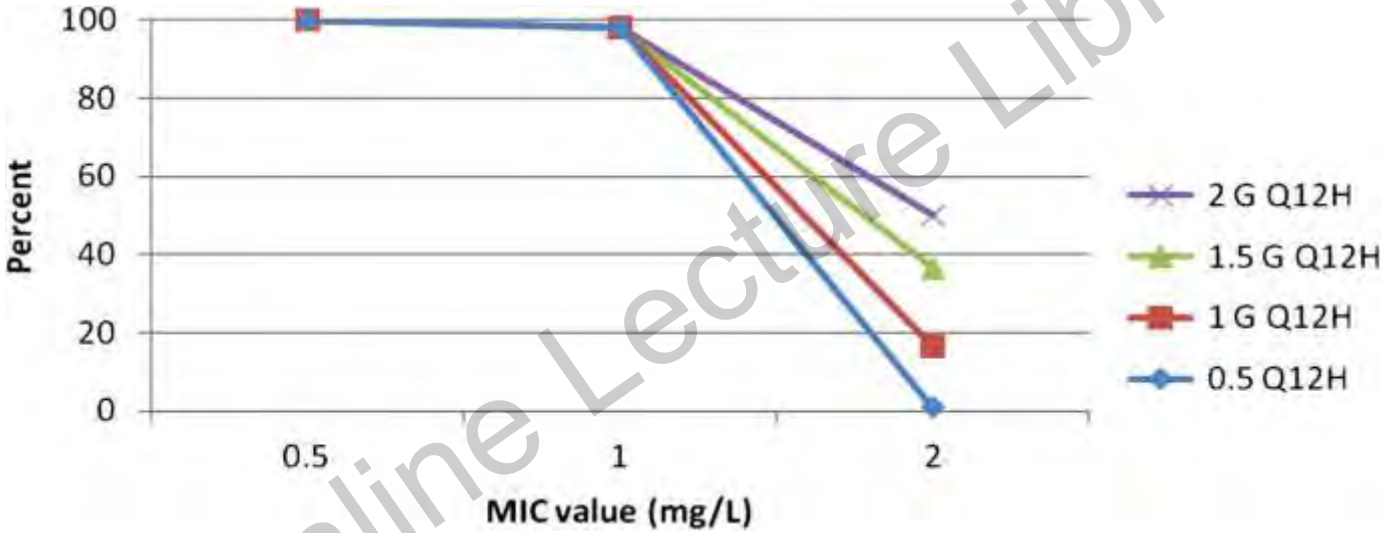
Pneumonia N=59	Bacteremia, Endocarditis N=320	Bacteremia, Endocarditis N=50	Septic Shock N=65	Bacteremia N=182
Single Center	Single Center	Single Center	Multiple Centers	Multiple Centers
≥350 Failure=37%	≥421 Failure=49%	≥211 Failure=19%	≥451 Failure=33%	>373 Failure=16%
<350 Failure=68%	<421 Failure=61%	<211 Failure=63%	<451 Failure=82%	≤373 Failure=28%
P-value 0.004	P-value 0.038	P-value 0.02	P-value 0.003	P-value 0.043

PK/PD Goal = 24-Hr AUC/MIC ≥ 400

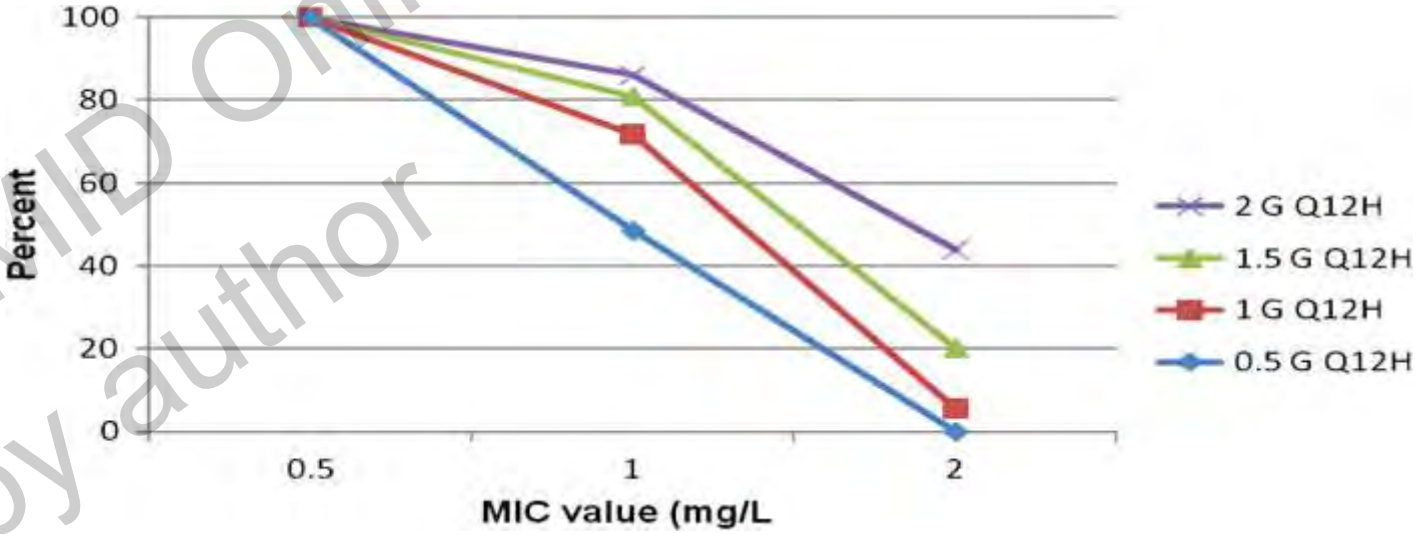
(1) Moise-Broder et al Clin Pharmacokinet 2004; 43:925; (2) Kuller et al Clin Infect Dis 2011; 52:975; (3) Brown et al Antimicrob Agents Chemother 2012; 56:634; (4) Zelensky et al Int J Antimicrob Agents 2013; 41:255; (5) Holmes et al Antimicrob Agents Chemother 2013; 57:1654

Probability of Achieving AUC/MIC Ratio ≥ 400

Trough 15-20 mg/L



Trough 10-15 mg/L



Patel et al Clin Infect Dis 2011; 52:969

Vancomycin Trough Concentration and Poor Outcomes

Trough (Cmin) Values	Vancomycin Failure (%)	P vs REF	Nephrotoxicity (%)	P vs REF
<10 mg/L	46/70 (66%)	0.001	10/65 (15%)	0.682
10-14.9 mg/L	52/90 (58%)	0.016	13/76 (17%)	0.476
15-20 mg/L	34/86 (39%)	REF	10/77 (13%)	REF
>20 mg/L	31/62 (50.0%)	0.206	17/62 (27%)	0.032

Nephrotoxicity was significantly higher in vancomycin failures (20% vs 11%); Nephrotoxicity higher with concomitant aminoglycosides (20% vs 11%)

Kuller et al Clin Infect Dis 2011; 52:975

Vancomycin and Nephrotoxicity

- Systematic review of 15 studies evaluating vancomycin troughs of 15-20 mg/L versus lower values
- Higher troughs associated with higher odds ratio (2.67; CI 1.95 to 3.65) for nephrotoxicity. Risk persisted after adjustment for other causes of nephrotoxicity
- Longer duration of therapy also increased rate of nephrotoxicity
- Most nephrotoxicity was reversible and few patients (3%) required dialysis

Van Hal et al Antimicrob Agents Chemother 2013; 57:734

Continuous Versus Intermittent Infusion of Vancomycin

- Systematic reviews and meta-analysis of 1 prospective trial and 5-11 retrospective studies
- Overall mortality was not different between the two groups in either review
- Conflicting results in terms of safety between continuous and intermittent infusion
- One review showed a significantly lower risk of nephrotoxicity with continuous infusion, but 2 of 5 studies had a 12-14% lower exposure (total AUCs) with continuous infusion

Cataldo et al J Antimicrob Chemother 2012; 67:17
Dimondi & Rafferty Ann Pharmacother 2013; 47:219

Mortality and Vancomycin MICs >1.0 mg/L by BMD or >1.5 mg/L by Etest

- 3 published systematic reviews and meta-analyses of high versus low vancomycin MICs
- Mortality significantly higher in patients infected with MRSA strains with a vancomycin MIC >1 mg/L by BMD and >1.5 mg/L by Etest
- Mortality predominately driven by bloodstream infections
- 170 patients with MIC>1 matched 1:1 for daptomycin and vancomycin treatment had lower 30-day mortality (4% vs 13%) and persistent bacteremia (19% vs 42%) with daptomycin

van Hal et al Clin Infect Dis 2012; 54:755; Jacob & Diazgranados Int J Infect Dis 2013; 17:e93; Marvos et al Int J Antimicrob Agents 2012; 40:496; Murray et al Clin Infect Dis 2013; 66:1562

Thank you for your attention