



National Pathology Support Services



# The method of parenteral antibiotic administration: Is it a big issue ?

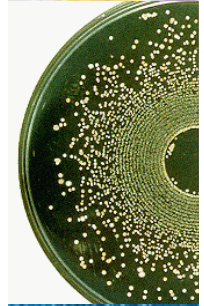
**Adrian Brink**

**Clinical Microbiologist, Ampath National Laboratory  
Services, Milpark Hospital, Johannesburg**

# Scope of presentation



- Introduction
- Does continuous infusion impact on *clinical outcome* in critically ill patients?
- Latest data
- Does continuous or prolonged infusion impact on *resistance*?
- Stability of beta-lactams after reconstitution
- Conclusions





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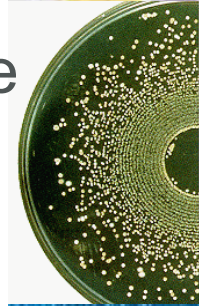


# Introduction

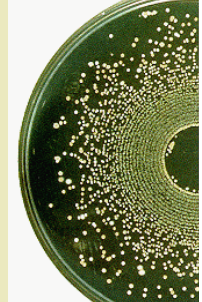
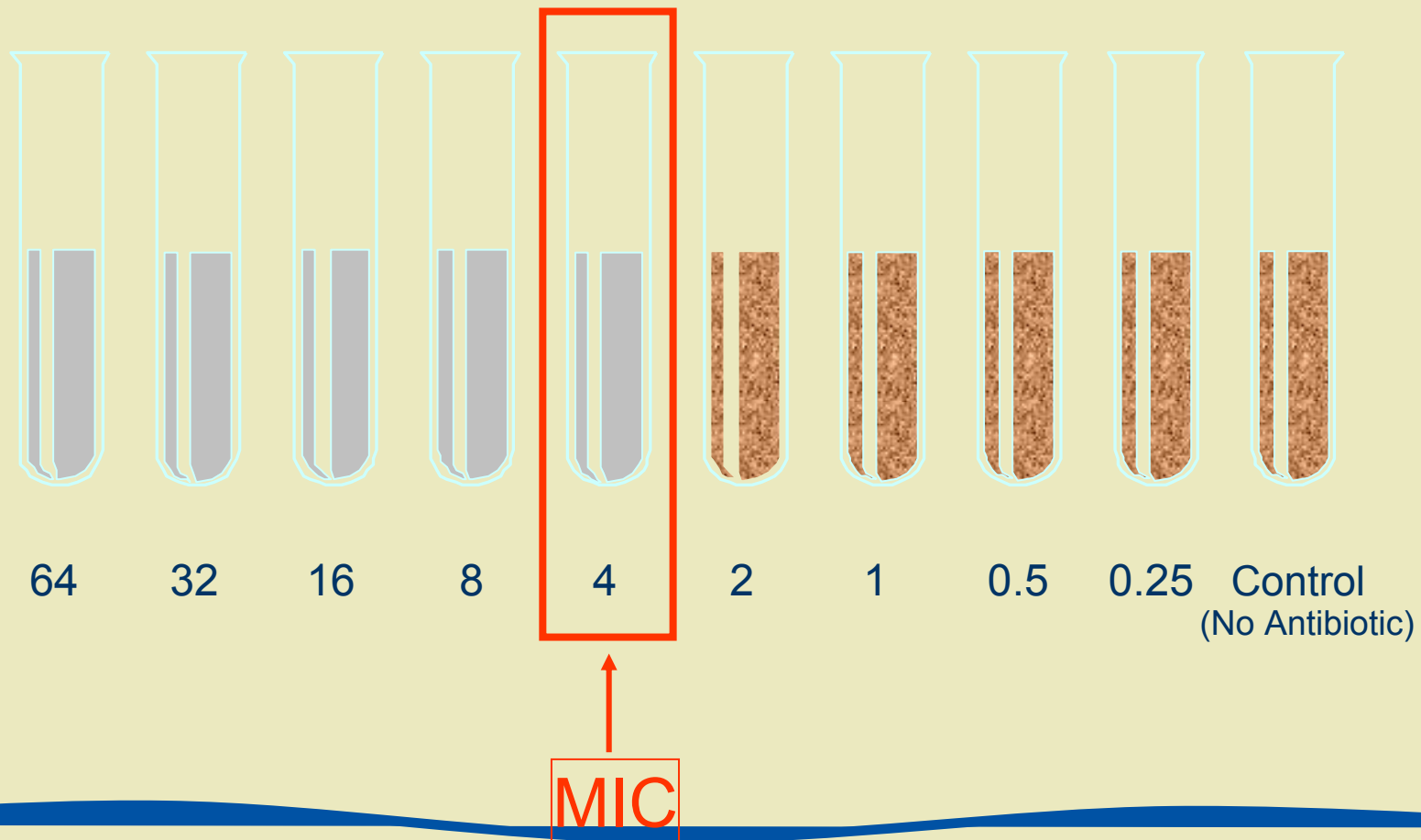
# Application of PK/PD



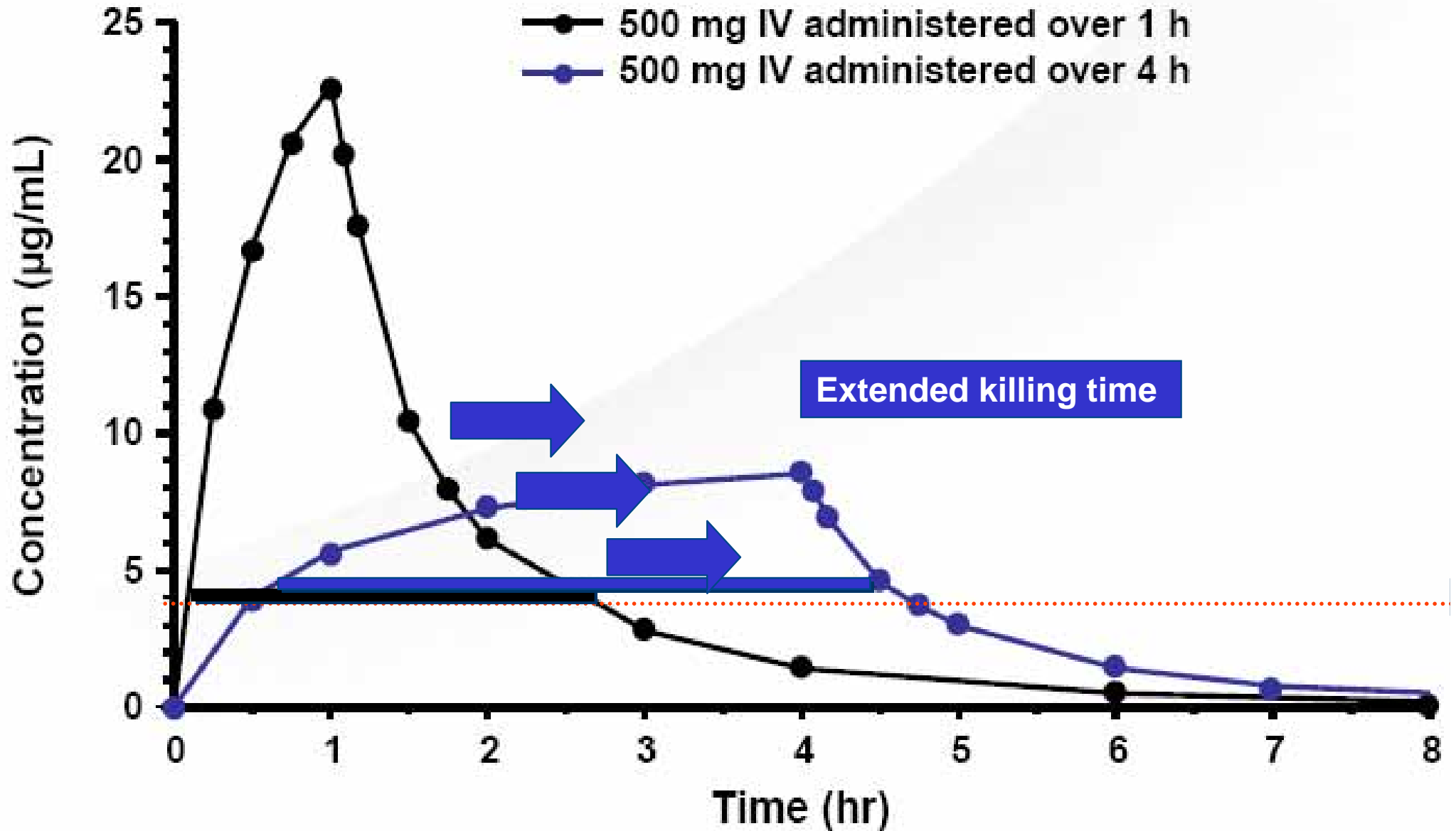
- Desired target for most  $\beta$ -lactams = *maximal effect* is achieved at 4 times the MIC of the pathogen.
- Most authors agree that  $T > MIC$  has to be at least 40-50% of the dosing interval to achieve clinical effectiveness.
- Maximal killing is seen when  $T > MIC$  is up to 60-70%
- As MIC`s of the pathogens to be treated increase there is a lower probability that a fixed dose will attain desired target



# Determining Minimum Inhibitory Concentration



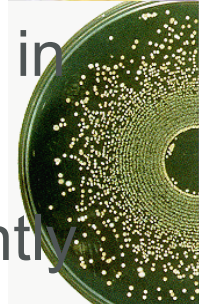
# Prolonged infusion



# PK/PD in critically ill patients



- In ill patients, PK are different and chances that desired target is reached, is also lower:
  - ~ rate and extent of tissue penetration of imipenem is decreased in critically ill patients<sup>1</sup>
  - ~ penetration of meropenem into infected tissues show significantly lower free concentrations in the lung vs serum<sup>2</sup>



<sup>1</sup>Tegeder *et al. Clin Pharmacol Ther* 2002;71 :325-333

<sup>2</sup>Tomaselli *et al. Antimicrob Agents Chemother* 2004;48:2228-2232

# Practical parameters



- 2 parameters - Trough ( $C_{min}$ ) from an bolus dose  
vs  
steady state ( $C_{ss}$ ) during continuous/prolonged infusion.
- $\Delta C_{ss} > C_{min}$  in all instances, up to a factor of 8





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# Historical data

# Application of PK/PD: Gram-negative R<sub>x</sub>- VAP



- Bacteriological efficacy in 30 ICU patients with nosocomial pneumonia
- Clear correlation between length of time that serum concentrations exceeded the MIC and time to eradicate the pathogen
- If dosage was changed to achieve a longer time above MIC, the time to achieve bacterial eradication in these severely ill patients was shorter



# Continuous infusion: Ceftazidime



- Most extensively studied: CI vs II<sup>1,2,3</sup>
- 3g over 24h
- Safe and effective in:
  - ~ neutropenic<sup>4</sup>
  - ~ critically ill patients<sup>5</sup>



<sup>1</sup>Lemmen *et al.* *J Antimicrob Chemother* 1997;39:841-842

<sup>2</sup>Mouton *et al.* *Antimicrob Agents Chemother* 1990;34:2307-2311

<sup>3</sup>Nicolau *et al.* *Antimicrob Agents Chemother* 1996;40:61-64

<sup>4</sup>Daenen *et al.* *Eur J Clin Microbiol* 1995;14:188-192

<sup>5</sup>Benko *et al.* *Antimicrob Agents Chemother* 1996;40:691-695

# Continuous infusion: Piperacillin/tazobactam



- Recently<sup>1,2</sup>:

~ *Standard infusion* time of 30 minutes:

dose of 3.375 g 4/d achieves T>MIC of 50% for bacteria with MIC's < or = 2mg/l

~ *Prolonged infusion* (4 hours):

dose of 3.375 g 3/d achieves T>MIC of 50% for bacteria with MIC's of 16mg/l



<sup>1</sup>Grant *et al. Pharmacother* 2002;22:471-483

<sup>2</sup>Lomaestro *et al.* 2002 Abstract A-2190 42<sup>nd</sup> ICAAC San Diego

# Continuous infusion: Meropenem



- *In vitro* model of continuous infusion<sup>1</sup>
    - ~ Evaluation of corresponding killing curves showed improved antimicrobial activity of 1g/24h of continuous infusion vs 1g 8-hourly of bolus dosing
  - Critically ill patients<sup>2</sup>
    - ~ 2g loading dose, followed by a 3g continuous infusion (CI) (new solutions prepared every 8 hours)
- vs
- ~ Intermittent infusion 2g 8-hourly (II)
  - ~ CI: Mean meropenem concentration  $11.9 \pm 5.0$  mg/l
  - ~ II: Mean trough levels  $8.5 \pm 1.0$  mg/l ( $P < 0.001$ )
  - ~ No problems with stability neither toxicity or S/E



<sup>1</sup>Keil et al. Antimicrob Agents Chemother 1997;41:1215-1219

<sup>2</sup>Thalhammer FF, et al. J Antimicrob Agents 1999;43:523-527



**Does continuous infusion impact  
on clinical outcome in critically ill  
patients?**

# General outcome ?



- Pyrexia
- Leucocytosis
- Duration of mechanical ventilation
- LOS ICU or hospital
- Adverse events

~ No difference vs bolus infusion



# Clinical cure ?

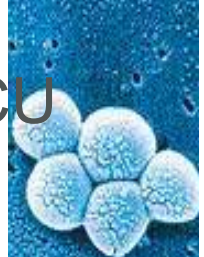
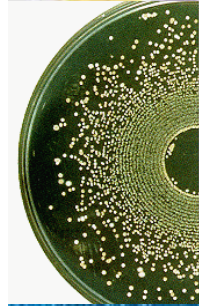


- Clinical cure (Resolution of Sx & Sx):

- ~ Until recently most investigators found no difference

- ~ Increased rate of clinical cure found in infusion group with meropenem for VAP patients<sup>1</sup>

- ~ ITT: significant incidence of cure in infusion group in those ICU patients who had received at least 4 days of ceftriaxone Rx<sup>2</sup>



<sup>1</sup>Lorente *et al. Ann Pharmacother* 2006;40:219-223

<sup>2</sup>Roberts *et al. J Antimicrob Chemother* 2007;59:285-291

# Mortality?



- Mortality:
  - ~ no difference vs bolus for
    - ..... ceftazidime (septicaemic meliodosis)<sup>1</sup>
    - ..... piperacillin (septic critically ill)<sup>2</sup>
    - ..... ceftriaxone (critically ill)<sup>3</sup>
    - ..... cefepime (critically ill)<sup>4</sup>
    - ..... piperacillin-tazobactam (cIAI)<sup>5</sup>
  - ~ in older studies mortality was 2<sup>o</sup> outcome,  
not powered to detect change in mortality



<sup>1</sup>Angus *et al.* *Br J Clin Pharmacol* 2000;50:184-191

<sup>2</sup>Rafati *et al.* *Int J Antimicrob Agents* 2006;28:122-127

<sup>3</sup>Roberts *et al.* *J Antimicrob Chemother* 2007;59:285-291

<sup>4</sup>Georges *et al.* *Int J Clin Pharmacol Ther* 2005;43:360-369

<sup>5</sup>Lau *et al.* *Antimicrob Agents Chemother* 2006;50:3556-3561

# Cost effectiveness ?



- Cost effectiveness

- ~ Level I costs (cost of actual antibiotics)
- ~ Level II costs (drug, preparation, admin costs of study drug, concomitant antibiotics to treat the infection, adverse events, Rx failure)

- ~ Significantly lower than bolus group ( $P < 0.001$ )
- ~ Level I:  $432 \pm 354$  vs  $786 \pm 354$  U\$ for bolus
- ~ Level II:  $627 \pm 387$  VS  $1007 \pm 429$  U\$ for bolus





# Latest studies..... Continuous or prolonged infusion

# SYSTEMATIC REVIEW

## BOLUS vs CI



REVIEW ARTICLE

Drugs 2005; 65 (17): 2499-2511

0012-5667/05/0017-2499/\$39.95/0

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## Continuous versus Intermittent Intravenous Administration of Antibacterials with Time-Dependent Action

A Systematic Review of Pharmacokinetic and Pharmacodynamic Parameters

Sofia K. Kasiakou,<sup>1,2</sup> Kenneth R. Lawrence,<sup>3</sup> Nicolaos Choulis<sup>4</sup> and Matthew E. Falagas<sup>1,5,6</sup>

In conclusion, the reviewed data suggest that the continuous intravenous infusion of antibacterials with time-dependent bacterial killing seems to be superior than the intermittent intravenous administration, from a pharmacodynamic point of view, at least when treating bacteria with high MIC values for the studied antibacterials.



# Cefepime



- Cefepime, 4g continuous infusion over 24 hours
- Critically ill ventilated patients with nosocomial pneumonia
- Both serum and epithelial lining fluid concentrations exceeded MIC of infecting pathogens for entire dosing interval; 100% T>MIC

Δ Optimizes PK/PD of cefepime =optimal bactericidal activity



# Piperacillin/tazobactam



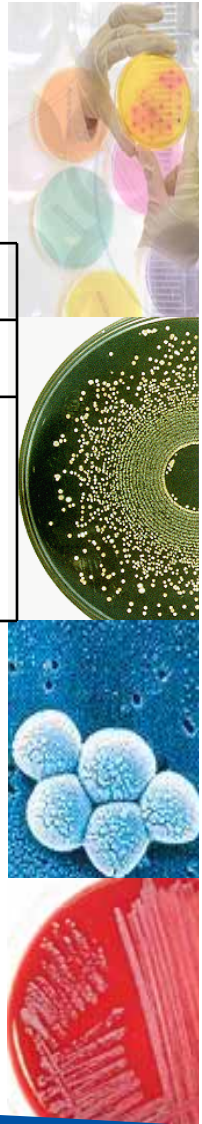
- n= 98 patients were evaluated (47 received continuous infusion, 51 received intermittent infusion -3.375 g 6h or 4.5 g 8h )

	Standard Regimen	Nosocomial Regimen*
<b>Loading dose</b>	2.25 g/30 min	2.25 g/30 min
<b>Continuous infusion</b>	$Cl_{cr} \geq 20$ mL/min <b>9g/150 mL NS at 7 mL/h</b>	$Cl_{cr} > 40$ mL/min <b>13.5 g/150 mL NS at 7 mL/h</b> $Cl_{cr} = 20-40$ mL/min <b>9 g/150 mL NS at 7 mL/h</b>

\*Nosocomial infections, including suspected *P. aeruginosa* infection, were defined as an infection that developed  $\geq 48$  h after admission.

- Demographic characteristics were similar with the exception of a greater number of patients with urosepsis or bacteremia in the continuous-infusion regimen ( $P = 0.010$ )

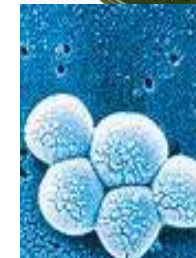
Grant *et al. Pharmacotherapy* 2002;22(4):471-483.



# Piperacillin/tazobactam



	Continuous infusion	Bolus infusion	P value
Clinical response	94% (44/47)	82% (42/51)	$P = 0.081$
Microbiological response	89% (25/28)	73% (23/32)	$P = 0.092$
Duration of Rx	$7.3 \pm 4.8$	$8.7 \pm 7.1$	$P = 0.26$
Days to defervescence of fever ( $<101.0^{\circ}$ F)	$1.2 \pm 0.8$	$2.4 \pm 1.5$	$P = 0.012$
Mean number of days for leucocytosis normalization	$2.8 \pm 2.4$	$3.9 \pm 2.2$	$P = 0.065$



## A better way to dose pip/taz ?

- Comparison of two dosing regimens for serious *P. aeruginosa* infections
  - ~ 3.375 grams IV over 30 minutes 6/d (4 hourly)
  - ~ 3.375 grams IV over 4 hours 3/d (8 hourly)



# Piperacillin/tazobactam



Characteristic	Extended infusion (n=102)	Intermittent infusion (n=92)	P-value
Primary source of culture sample:			
Respiratory tract	55 (53.9)	48 (52.2)	0.8
Skin or soft tissue	11 (10.8)	23 (25.0)	0.009
Mean duration of therapy (days ± SD)	8.4 (4.4)	8.4 (4.5)	0.9
Concomitant AG therapy	21 (22.8)	26 (25.5)	0.6
Concomitant FQ therapy	5 (5.9)	10 (10.9)	0.2



# Piperacillin/tazobactam



Patients with APACHE score  $\geq 17$

14d. Mortality:

30 minute infusion

31.6%

4 hour infusion

12.2%  $p=0.04$

Median LOS (days):

30 minute infusion

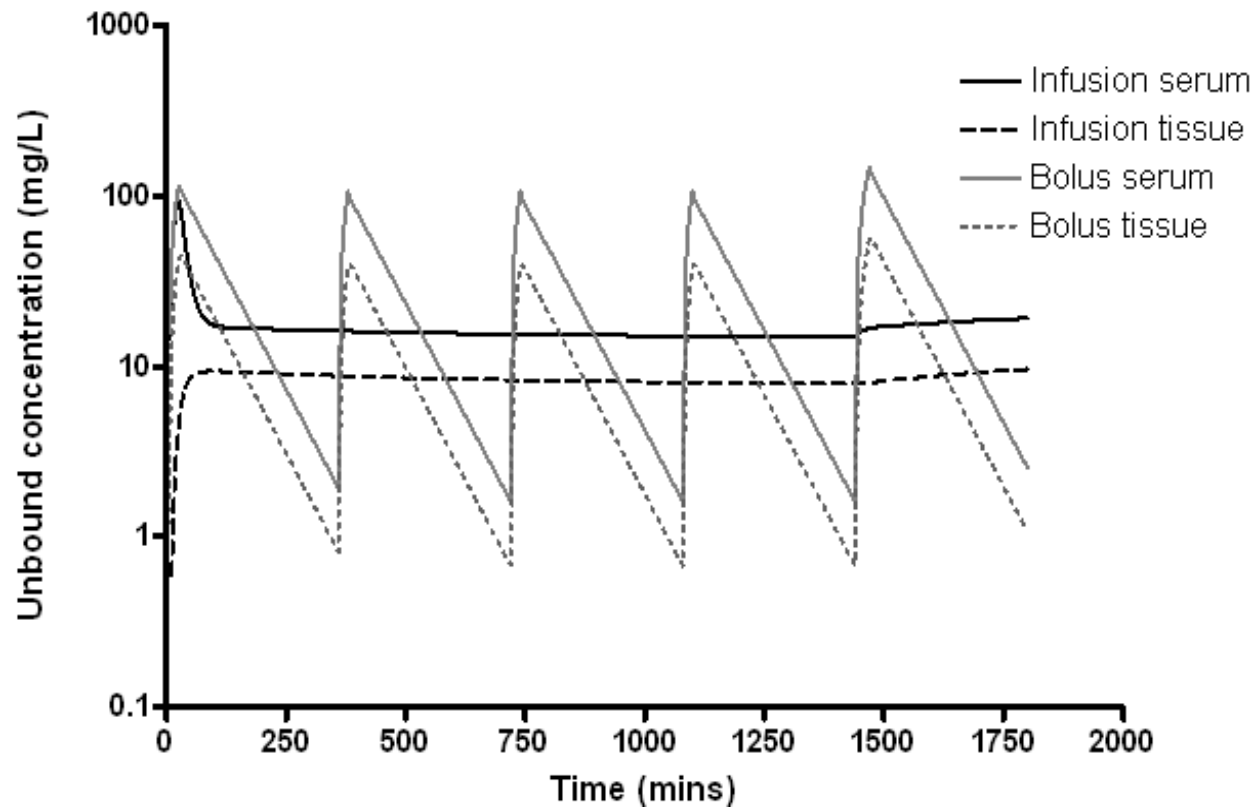
38

4 hour infusion

21  $p=0.02$



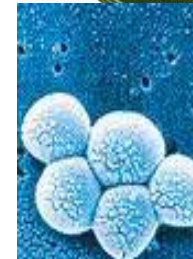
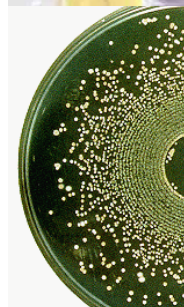
# Piperacillin/tazobactam



# Piperacillin/tazobactam

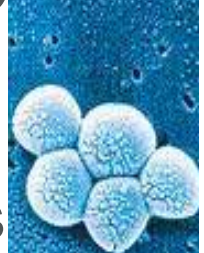


- On D2, significantly higher median plasma concentrations in infusion group vs bolus group were recorded (16.6 vs 4.9 mg/L;  $P=0.007$ )
- The data in this study shows reduced variability of steady-state concentrations using continuous infusion
- This enables the intensivist to dose the patient with greater confidence for achieving target concentrations



## A better way to dose pip/taz ?

- Same group in another study
  - ~ 3.375 grams IV over 30 minutes 3-4/d (n=59)
  - ~ 3.375 grams IV over 4 hours 3/d (n=70)
- 30-day mortality & LOS was similar 8.5% vs 5.7% ( $P=0.54$ )
- BUT only 4 and 7% of patients were in ICU, mean Apache was 10.5 & 10.9 & 59.3 and 58.6 % of infecting pathogen's MIC's were < 8mg/L, respectively



# Meropenem



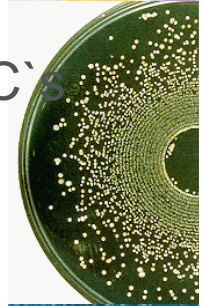
- ~ A model using PK properties of meropenem, susceptibility results (*P.aeruginosa*, n=208, 810-bed hospital in Connecticut) and Monte Carlo simulation was used to analyse 4 different dosing regimens of meropenem at PD endpoints
- ~ Effect of adding aminoglycoside was also evaluated
- ~ 1g 8h & 2g 8h  
vs  
1g 8h infused over 3 h & 2g 8h infused over 3 h
- ~  $\Delta$  Meropenem 2g 8h with a 3-h infusion in combination with aminoglycosides provides the greatest likelihood of *P.aeruginosa* coverage that might be less susceptible to meropenem and may prevent further resistance development



# Meropenem



- ~ 500mg bolus 8-hourly & 250mg loading dose followed by 1.5g CI over 24 hours  
vs 1g bolus 8-hourly vs 500mg loading dose followed by 3g CI over 24 hours
- ~ Probability of achieving target by MIC for high and low dose CI were MIC's of 4 and 2mg/l respectively
- ~ Corresponding values for II were only 0.5 and 0.25mg/l respectively
- ~ Bolus infusion therefore results in adequate activity against *K.pneumoniae* and *E.aerogenes* (>90% of strains MIC ≤ 0.25mg/l)
- ~ However, against *P.aeruginosa* bolus infusion doesn't and a clear advantage is shown of high-dose Rx using continuous infusion (<30% of strains MIC ≤ 0.25mg/l)



# Meropenem



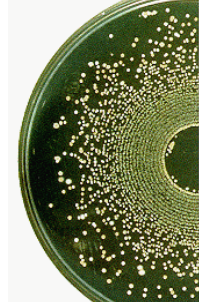
~ VAP patients



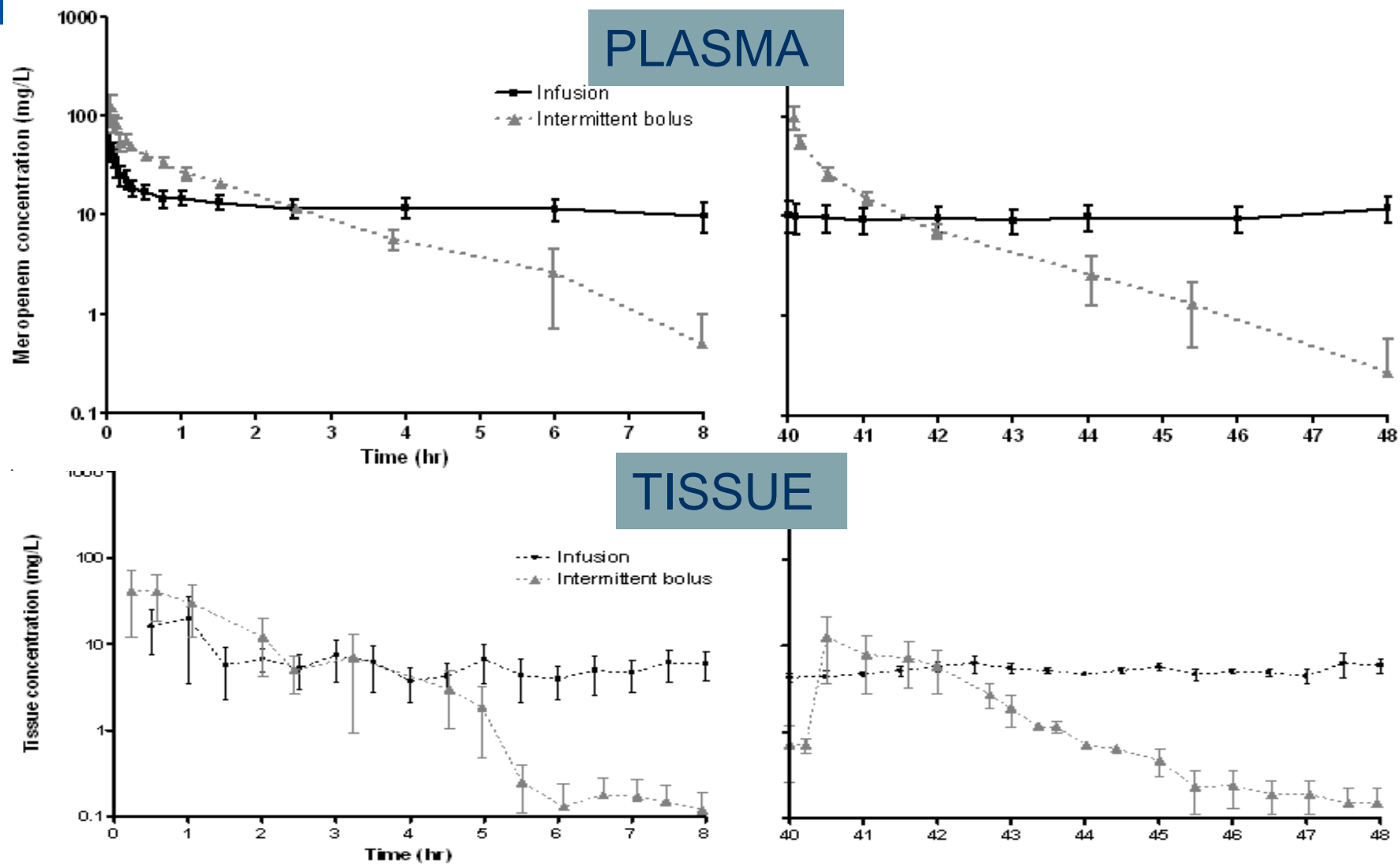
% T>MIC	16	8	4	1
<b>1g 8h as bolus</b>	<b>28 %</b>	<b>45 %</b>	<b>57 %</b>	<b>74 %</b>
<b>1g 8h over 3 hours</b>	<b>37 %</b>	<b>58 %</b>	<b>72 %</b>	<b>93 %</b>
<b>2g 8h over 3 hours</b>	<b>57 %</b>	<b>72 %</b>	<b>85 %</b>	<b>98 %</b>

CLSI 2007: R  $\geq$  16, IR = 8, S  $\leq$  4

~ For the Rx of infections caused by pathogens such as *P.aeruginosa* with possible resistance, a 3-h infusion of 2g meropenem every 8 h provide serum concentrations above MIC of 16 mg/l for almost 60% of dosing interval



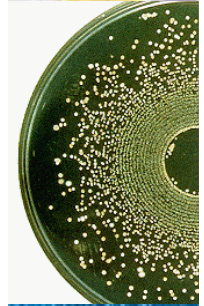
# Meropenem: Microdialysis



# Meropenem



- Superior obtainment of PD targets was achieved using continuous or prolonged infusion against less susceptible *P.aeruginosa* & *A baumannii*



# Meropenem



- Retrospective cohort study of patients with VAP caused by GNBs who received initial empiric therapy with meropenem
- Two cohorts
  - Meropenem 1 gram infusion over 6 hours 4/d (n=42)
  - Meropenem 1 gram over 30 minutes 4/d (n=47)



# Meropenem



## Prolonged vs Bolus

### Clinical cure

~ All VAP pts      **90.5%** vs 59.6%      (average 45-65%)

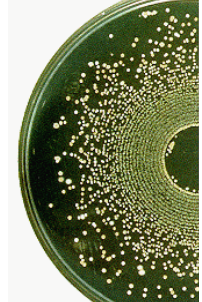
OR 6.44;  $p < 0.001$

~ *P.aeruginosa*      **84.6%** vs 40%      (average 29-37%)

OR 8.25;  $p = 0.02$

~ MIC  $\geq 0.50$   $\mu\text{g/ml}$       **80.95%** vs 29.41%

OR 7.84;  $p = 0.003$



# Imipenem



*Journal of Antimicrobial Chemotherapy*  
doi: 10.1093/jac/dkn543

JAC

## Comparison of the pharmacodynamics of imipenem in patients with ventilator-associated pneumonia following administration by 2 or 0.5 h infusion

Sutep Jaruratanasirikul\* and Teeratad Sudsai

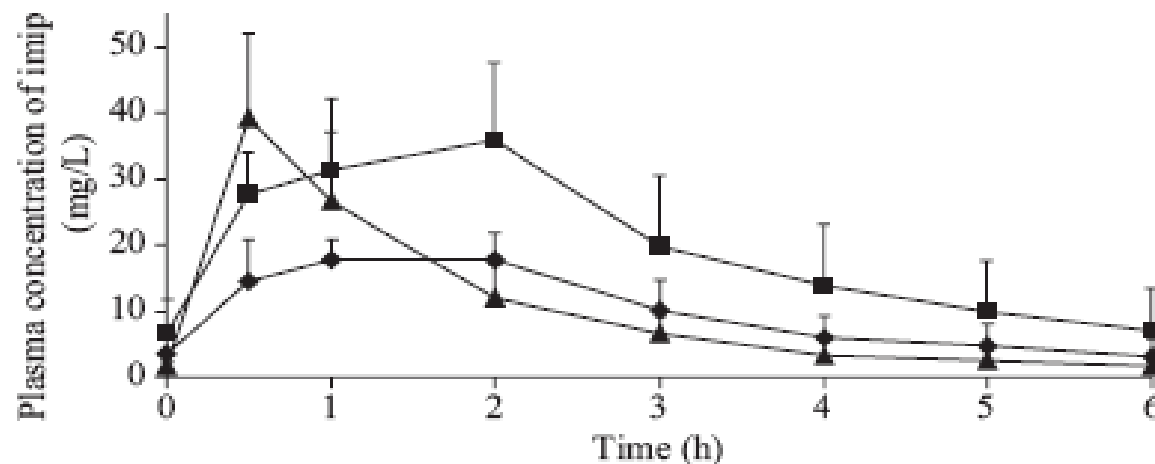
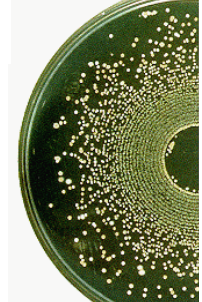


Figure 1. Mean plasma imipenem concentration–time data for nine patients with VAP following administration of: 0.5 g, 0.5 h infusion (filled triangles); 0.5 g, 2 h infusion (filled diamonds); and 1 g, 2 h infusion (filled squares).



# Imipenem



- The 2h infusions of imipenem resulted in greater T>MIC than the 0.5h infusion
- For infections caused by pathogens with high MIC's, a 2h infusion of 1g imipenem 6-hourly provides plasma concentrations above the MIC of 4 mg/L\* for 60% of a 6-hourly dosing interval

\* Breakpoint for susceptibility



# Linezolid



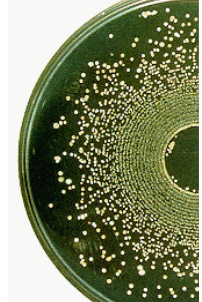
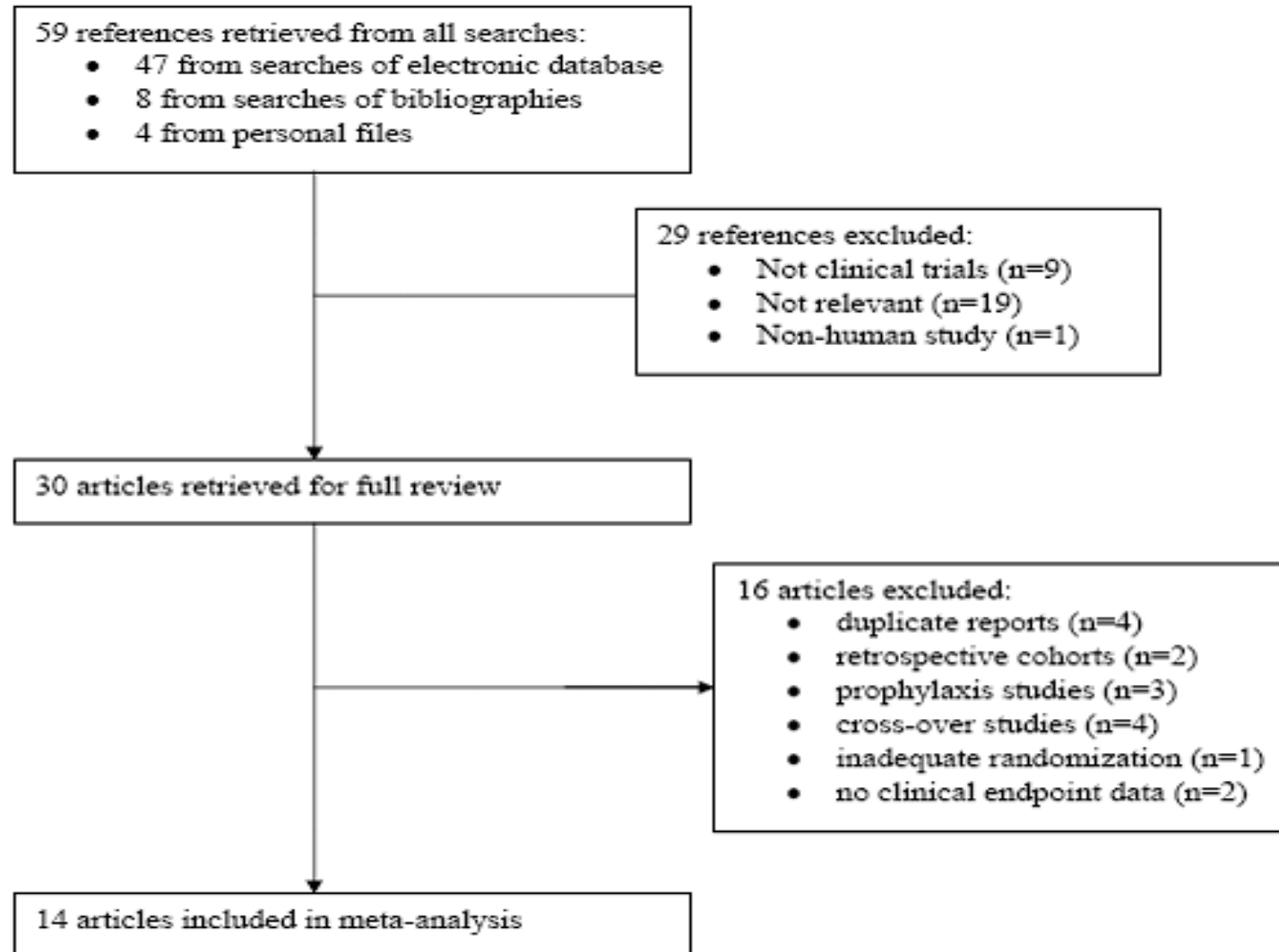
- CI of 300mg loading dose, followed by 900mg on D1 & 1200mg thereafter (n=8) vs BD bolus infusion (n=8) in critically ill patients with sepsis
- Mean C<sub>min</sub> 1.1 ± 1.5 mg/L bolus infusion vs serum concentration of 7.3 ± 4.3 mg/L in CI group after 12h ( $P < 0.01$ )
- At 72h 2.5 ± 3.1 vs 10.6 ± 4.5, respectively ( $P < 0.01$ )
- Levels much lower than described in healthy volunteers with conventional dosing
- Conventional dosing more likely not to achieve AUC/MIC ratio targeted for positive outcome (80-120) whereas CI did



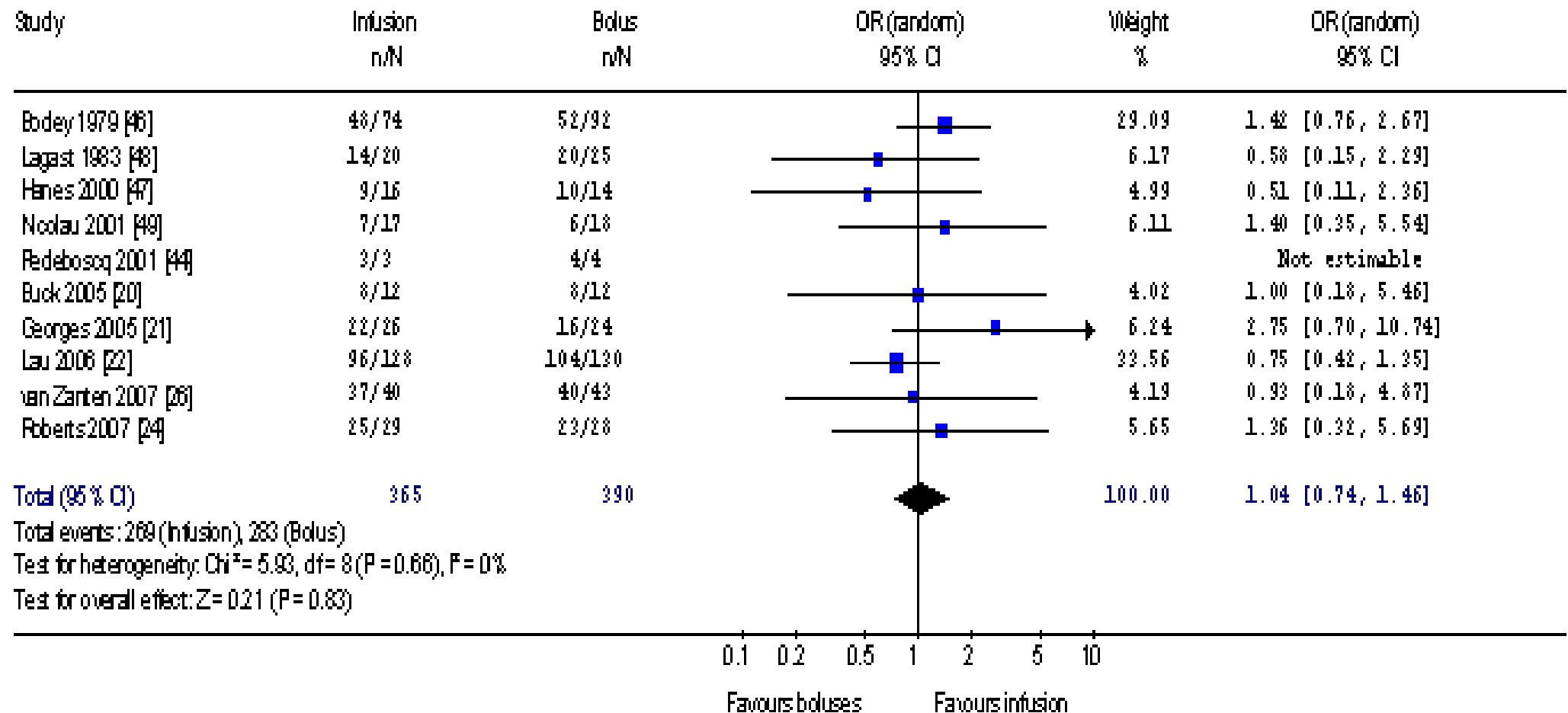


**But a recent meta-analysis found  
equivalent clinical outcomes.....**

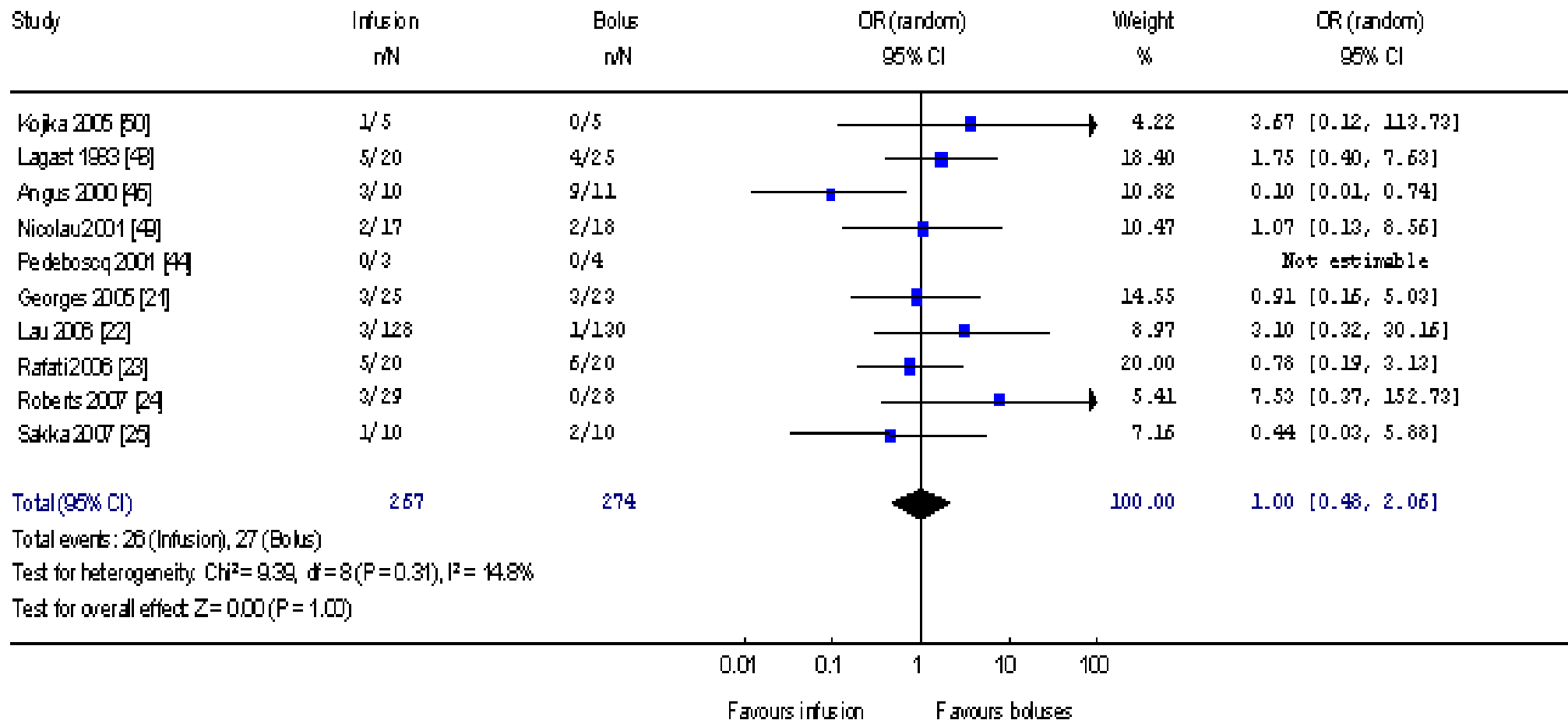
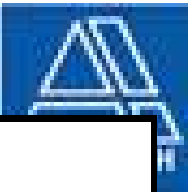
# Meta-analysis



# Meta-analysis – Clinical cure



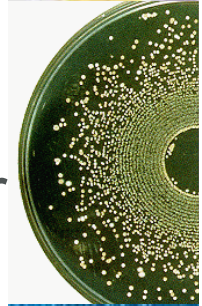
# Meta-analysis – Mortality



# Meta-analysis



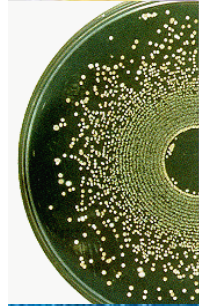
- The meta-analysis has found equivalent clinical outcomes when  $\beta$ -lactam antibiotics are administered by extended- or continuous-infusion.
- The limited data available suggests that continuous infusion of  $\beta$ -lactam antibiotics leads to the same clinical results as higher dosed bolus administration in hospitalized patients.



# Comment on meta-analysis



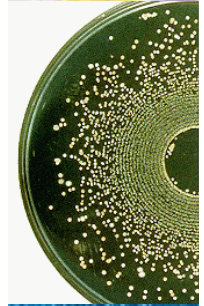
- Many such publications were reported from studies in late 20th century/early 21st when Gram-negatives were “tame” ...so even bolus infusion lead to target attainment because MIC's were probably low then.
- These studies not powered to detect changes in mortality
- Some studies used loading doses and others not.
- Maybe as GNB MIC's have increased, CI or prolonged or extended infusions will be necessary to reach adequate  $T > MIC$ .
- Regarding the latter, prolonged infusion have shown to offer significant benefit in subsets of *P.aeruginosa* infected patients



# Comment on meta-analysis



- Besides outcome, resistance development might be another reason we should consider prolonged or continuous infusions





**Does prolonged/continuous  
infusion impact on resistance  
development in critically ill  
patients?**

# Doripenem vs Imipenem



- Doripenem 500mg over 4 hours every 8 hours  
vs.  
Imipenem 500-1000 mg over 30-60 minutes every 6-8 hours
- Phase III trial: 531 patients with VAP
- Clinical cure rates: 68.3% (Dori) vs 64.8% (Imi) – n=249; difference 3.5%; 95% CI, -9.1%-16.6%
- All cases: clinical cure was higher with doripenem than imipenem at higher APACHE II & older age)



# Subset of *Pseudomonas* infected patients



	Dori		Imi
Baseline susceptibility	100% (28/28)		76% (19/25)
Clinical cure rates	80% (16/20)	>	43% (6/14)
Development of R during therapy	18% (5/28)	<	50% (11/22)





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# Stability of beta-lactams after reconstitution

# Meropenem



Diluent	Hours stable up to 25°C	Hours stable at 4°C (fridge)
Vials constituted with water for injection for bolus injection	8	48
Infusions (1 - 20 mg/ml) prepared with: 0,9% sodium chloride	8	48
5% dextrose 5% dextrose and 0,2% sodium chloride 5% dextrose and 0,9% sodium chloride 5% dextrose and 0,15% potassium chloride 2,5% or 10% mannitol Normosol-M in 5% glucose	3	14
10% dextrose 5% dextrose and 0,02% sodium bicarbonate solution	2	8



# Imipenem



Diluent	Hours stable up to 25°C	Hours stable at 4°C (fridge)
Isotonic Sodium Chloride	4	24
5 % Dextrose in Water	4	24
10 % Dextrose in Water	4	24
5 % Dextrose & 0,9 % NaCl	4	24
5 % Dextrose & 0,45 % NaCl	4	24
5 % Dextrose & 0,225 % NaCl	4	24
5 % Dextrose & 0,15 % KCl	4	24
Mannitol 5 % and 10 % Vials constituted	4	24



# Piperacillin/tazobactam



## \* Reconstitution Directions

Diluents for Reconstitution:

Sterile Water for Injection

Bacteriostatic Water for Injection

Sodium Chloride Injection

## \* For intravenous infusion

The reconstituted solution may be further diluted to the desired volume (e.g. 50 ml or 100 ml) with one of the reconstitution diluents or with:

Dextrose 5% in Water

## \* Stability

Diluted solutions prepared for intravenous use are stable for **24 hours at room temperature (below 25 °C)** and 48 hours under refrigeration (2-8 °C) in I.V. bags or syringes





National Pathology Support Services

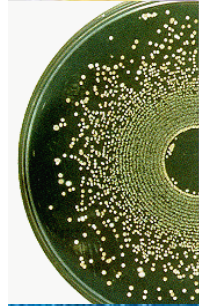


# Conclusion

# Conclusion



- Take note of instability of some drugs at room T°
- Need for additional IV line to prevent incompatibilities with other drugs
- Limited patient mobility due to presence of infusion pump
- Potential toxic breakdown products (ceftazidime)
- The exact role of CI/PI of beta-lactams in treatment of severe infections remains unclear



but

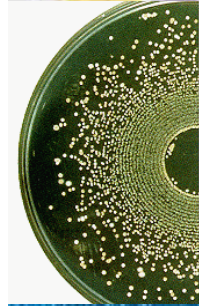
- Increasing evidence is emerging that suggests potential benefits



# Conclusion



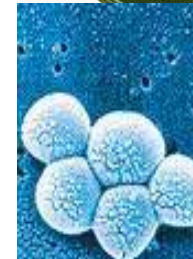
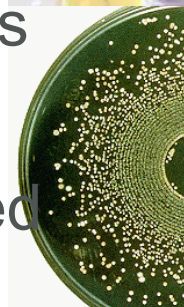
- When less susceptible bacteria are present, the opportunity for Rx failure is increased when using bolus infusion: consistent benefit for infecting pathogens with higher MIC's such as *P.aeruginosa*
- $\Delta$  Whether CI/PI will become another “ICU bundle” & whether it will truly impact on outcome needs to be resolved with more prospective clinical trials



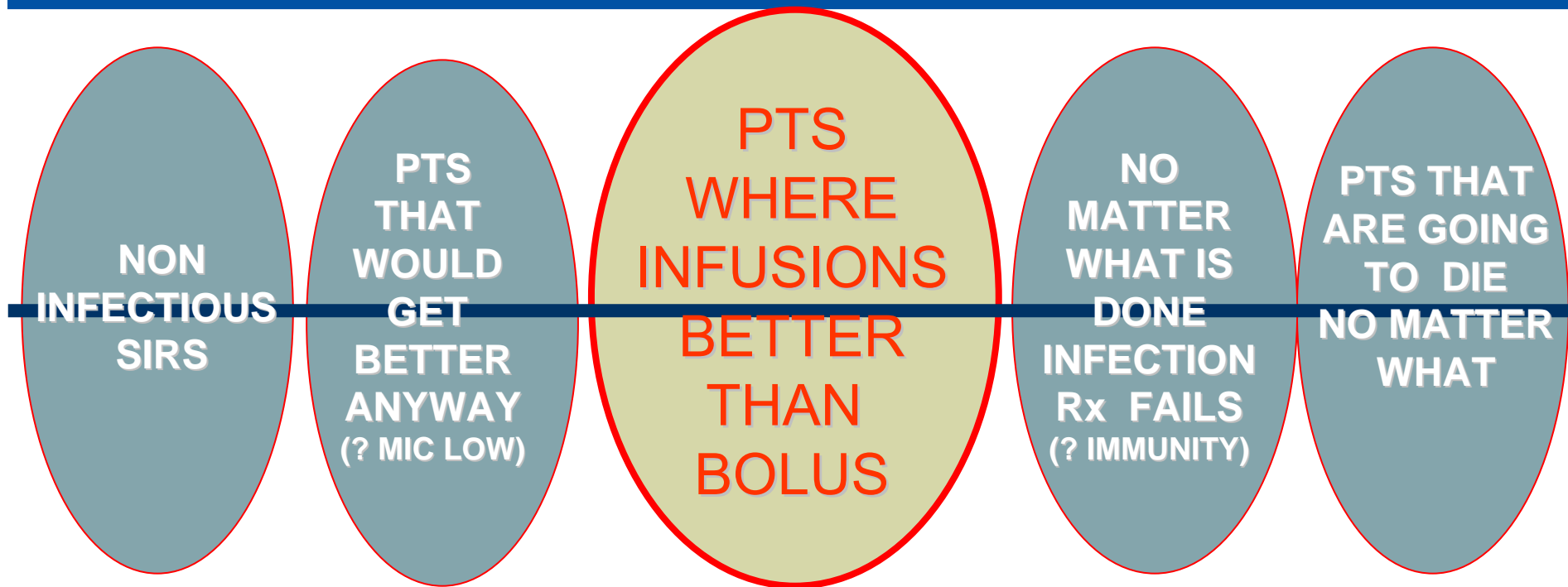
# Conclusion



- The exact role of CI/PI of beta-lactams in treatment of severe infections remains unclear but
- Increasing evidence is emerging that suggests potential benefits
- Particularly if patients are in *ICU* and *severely ill* and are infected with bacteria with *high MIC's*
  - reduced variability in achieving steady-state
  - greater chance of achieving target levels
- $\Delta$  Whether CI/PI will become another “Rx bundle” & whether it will truly impact on outcome needs to be resolved with more prospective clinical trials

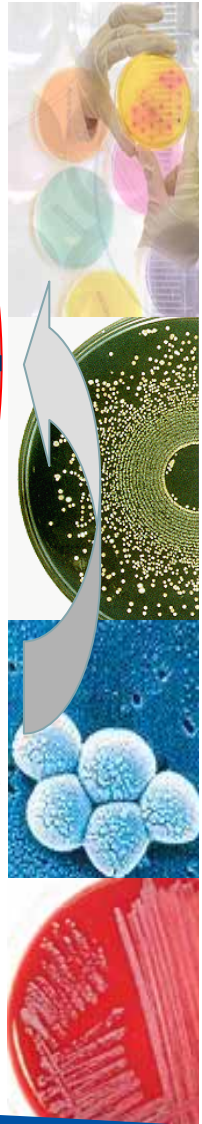


# Spectrum of patients treated with antibiotics



100 patient line

That's the group needed to demonstrate continuous infusions are better than bolus dosing



# Optimizing empiric therapy for nosocomial Gram-negative infections



- Choose beta-lactam core based on prior antibiotic exposure and susceptibilities:
  - ~ Don't use a beta-lactam that has been used in the last month
  - ~ Don't use a beta-lactam if there has been an isolate resistant to it in the last month
- In critically ill ICU patients, give the beta-lactam by prolonged/continuous infusion
- Combine the beta-lactam empirically with a large dose of an aminoglycoside
- Ask your lab for an MIC
- De-escalate therapy when susceptibilities available and/or dropping the aminoglycoside

