

Revisiting Beta-lactams – PK/PD improves dosing of old antibiotics

Alasdair MacGowan

Pre-clinical pharmacokinetic–pharmacodynamic assessments indicate Beta-lactam antibiotics have time-dependent killing, variable persistent antibiotic effects and that free drug $T > MIC$ is the dominant pharmacodynamic index. Prolonged or continuous infusion therapy has improved microbiological responses in pathogens with MICs at or 2–4 fold higher than existing EUCAST clinical breakpoints in pre-clinical studies. Human population pharmacokinetic modelling combined with Monte Carlo Simulation indicates improved pharmacodynamic target attainment rates and hence predicts improved clinical responses for those pathogens with raised MICs. However, the majority of human clinical trials comparing prolonged or continuous infusion to intermittent injection have failed to show superior clinical cures and for the most part microbiological successes. The exception being in various subgroup analyses. Future clinical trials need to focus on defining the $T > MIC$ sizes associated with clinical or microbiological cure in man, on those subgroups of patients where continuous, or prolonged infusion, is likely to be of greatest benefit, seek to reduce pharmacokinetic variability by the use of therapeutic drug monitoring and include measurement of the risks of emergence of resistance in target pathogens. At present, the clinical evidence base for prolonged or continuous infusion therapy is insufficiently strong to support widespread use.

Address

Bristol Centre for Antimicrobial Research & Evaluation, University of Bristol & North Bristol NHS Trust, Department of Medical Microbiology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

Corresponding author: MacGowan, Alasdair
(aldasair.macgowan@nbt.nhs.uk)

Current Opinion in Pharmacology 2011, 11:470–476

This review comes from a themed issue on
Anti-infectives
Edited by U. Theuretzbacher and J.W. Mouton

Available online 19th August 2011

1471-4892/\$ – see front matter
Published by Elsevier Ltd.

DOI [10.1016/j.coph.2011.07.006](https://doi.org/10.1016/j.coph.2011.07.006)

Introduction

The pharmacokinetics and pharmacodynamics of Beta-lactam drugs (penicillins, cephalosporins and carbapenems) have been extensively studied in pre-clinical infection models and numerous clinical studies in man. There is, therefore, a significant literature relevant to

both *in vitro*, *in vivo*, *in silico* and human trials findings. The basic pharmacodynamic properties of Beta-lactams imply that continuous infusion or prolonged infusion therapies (see definitions – Table 1) should have bacteriological and clinical advantages over intermittent injection when treating certain pathogens or infections. The topic of continuous infusion Beta-lactam therapy has been reviewed previously [1^{••},2,3^{••}]. In this review I will discuss the pre-clinical rationale for prolonged or continuous infusion B. lactam therapy as well as bringing the reported clinical experiences up to date. Finally, I will discuss the unresolved pre-clinical and clinical issues related to these therapeutic approaches.

Pre-clinical studies

The pre-clinical pharmacodynamics of Beta-lactam drugs have been well understood for over a decade [4] (Table 2). Antibacterial killing owing to Beta-lactams increases as drug concentrations increase below the pathogen MIC value and up to 4–5 times above the MIC. Bacterial killing at concentrations greater than these values does not increase with Enterobacteriaceae, *Staphylococcus aureus* or *Pseudomonas aeruginosa* [5,6]. Within the Beta-lactam family it has been proposed that penicillins, cephalosporins and carbapenems show different rates and degrees of bactericidal activity against Gram-negative pathogens with carbapenems being most rapidly bactericidal and penicillins least [7]. Persistent antibiotic effects have been exhibited with penicillins, cephalosporins and carbapenems against most Gram-positive pathogens including *S. aureus*, *Streptococcus pyogenes* and *S. pneumoniae*. By contrast, penicillins and cephalosporins have negligible persistent effects against *Escherichia coli*, *Klebsiella spp*, *Proteus spp* and *P. aeruginosa* [8[•]]. Carbapenems have persistent effects against both Gram-positive and negative pathogens [6].

The duration that the free Beta-lactam concentration is maintained over a crucial threshold, usually the MIC ($fT > MIC$), is the dominant pharmacodynamic index in determining B. lactam antibactericidal effect. $fT > MIC$ has been related to antibacterial efficacy of penicillins, cephalosporins and carbapenems against Gram-positive and negative pathogens [9].

It follows, therefore, that dosing strategies that optimise the $fT > MIC$ will improve antibacterial effect – especially for those pathogens with borderline susceptibility to existing intermittent doses. Alternatively, for more susceptible pathogens, a lower daily dose of drug will

Table 1**Proposed definitions of intermittent, prolonged and continuous intravenous infusion**

Intermittent injection	Infusion lasting 0.5–1 h
Prolonged infusion	Infusion lasting 3–4 h, usually 50% dosing interval
Continuous infusion	Infusion over a 24 h period at a fixed rate often preceded by a bolus dose.

be required. One approach to optimising $fT > MIC$ is the use of continuous infusion administration, or more frequent dosing in each 24 h period. More frequent Beta-lactam dosing has been shown to be advantageous in producing pathogen clearance by cephalosporins and carbapenems in animal and *in vitro* pharmacodynamic models. However, it is worth noting that such relationships may be only relevant over short term antibiotic exposures (up to 48 h) and data from a *Klebsiella* lung infection treated with a cephalosporin indicated that AUC/MIC was the best correlate to survival in long term dosing experiments [10*].

It is perhaps unsurprising that continuous infusion or prolonged infusion Beta-lactam therapy has been compared to conventional dosing in a variety of pre-clinical pharmacodynamic models. In an *in vitro* model continuous infusion ceftazidime was as effective as bolus injection for *P. aeruginosa* strains with low MICs but against strains with elevated MICs, continuous infusion (C_{ss} 20 mg/L) was superior [11]. Additional data have been reported with the carbapenems doripenem and meropenem – prolonged infusion doripenem (4 h duration) was as effective as intermittent injection for *P. aeruginosa* strains with $MIC \leq 2$ mg/L, however, 4 h infusion showed superiority for strains with MIC 4 mg/L and neither regimen was effective when MICs were ≥ 8 mg/L [12]. Similarly, simulations of high dose, prolonged infusion meropenem (2 g, 3 h infusion) were effective at clearing *P. aeruginosa* with MIC 8–16 mg/L from a pharmacokinetic model. Such strains are resistant using conventional clinical breakpoints [13].

The basic pharmacodynamic characteristics of B. lactams in terms of bacteriological effect are shown on Table 2, while the $fT > MIC$ targets for 24 h bacteriostatic effect and 2 log kill are summarised on Table 3.

Table 2**Pharmacodynamic characteristics of B. lactam antibiotics**

- Time-dependent killing by therapeutically achievable concentrations
- Minimal to moderate persistent antibiotic effects
- Maximising the duration of exposure optimises antibacterial effects
- Time above threshold amount of drug (for example MIC) is the dominant pharmacodynamic index

Table 3**Pharmacodynamic index sizes for 24 h bacteriostatic and bactericidal activity: data from the pre-clinical models**

	$fT > MIC\%$		
	Penicillins	Cephalosporins	Carbapenems
Enterobacteriaceae			
static	30–35	35–40	20–40
-2 log kill	–	–	35–55
<i>P. aeruginosa</i>			
static	30–35	25–40	20–45
-2 log kill	–	45–55	35–55
<i>S. pneumoniae</i>			
static	25–35	35–40	15–20
-2 log kill	35–45	–	25–40
<i>H. influenzae</i>			
static	25–35	–	–
-2 log kill	35–45	–	–
<i>S. aureus</i>			
static	15–35	20–30	10–30
-2 log kill	35–45	–	15–40

In the past 5 years a number of pre-clinical studies have been performed in order to better understand the pharmacodynamic drivers of emergence of resistance. The risk of resistance follows an inverse U-shape curve with drug exposure. No or little drug fails to promote resistance while large drug exposures result in bacterial death with out emergence of resistance [14,15]. The drug exposure that maximally drives resistance is usually that just below the 24 h bacteriostatic effect level [15]. In addition to exposure, time of drug exposure is crucial with longer drug exposures much more likely to result in emergence of resistance than short ones [15]. It is unclear whether the pharmacodynamic index that drives resistance is the same as $fT > MIC$, however, $fT > MIC$ can be related to risk of resistance [14,15]. In other studies risk of emergence of resistance to meropenem has been related to C_{min}/MIC and risk of resistance to a cephalosporin to AUC/MIC [14,16].

Human pharmacokinetics

The pharmacokinetic/pharmacodynamic characteristics of continuous infusion therapy in comparison to intermittent injection have been the subject of a systematic review for all antibacterials with a time-dependent action – most of these studies were of Beta-lactams [17**]. Seventeen randomised trials comparing continuous with intermittent infusion of the same antibacterial regimen were identified. The mean peak concentrations (C_{max}) of the intermittent administration was 5.5 times (range 1.9–11.2) higher than the concentration at steady state (C_{ss}) of the continuous infusion. Conversely, the trough concentration (C_{min}) of intermittent infection was on average 5.8 times (range 1.2–15.6) lower than C_{ss} . In three of six studies where the $T > MIC$ for the implicated pathogens was measured it was longer for the continuous infusion.

Table 4

Piperacillin-tazobactam MIC distributions of three key Gram-negative pathogens isolated from respiratory secretion or blood

MIC (mg/L)	E.coli		Enterobacter cloacae		P.aeruginosa	
	resp secretions (n=156)	blood (n=435)	resp secretions (n=116)	blood (n=156)	resp secretions (n=168)	blood (n=206)
0.25	1.0	0.2	0	0	1.2	0
0.5	11.8	0.5	3.9	0.6	1.2	0.5
1.0	42.4	6.4	26.3	3.8	4.2	1.1
2.0	23.2	55.6	42.1	32.7	15.2	2.6
4.0	11.3	21.6	9.7	39.7	47.0	55.0
8.0*	3.4	7.6	2.6	5.8	11.3	25.4
16.0*	2.0	2.5	6.6	3.8	7.3	10.1
	5.5		9.2		18.6	
	10.1		10.6		35.5	
32.0	1.5	1.4	3.9	3.2	7.1	4.2
64.0	0.5	1.1	2.6	7.7	2.4	1.1
128.0	1.0	0.7	2.6	1.3	1.2	0
256.0	3.0	2.5	0	0.6	1.2	0

*MIC values were prolonged/continuous infusion therapy most probably to improve outcomes.

Recently, a number of authors have used population pharmacokinetic modelling combined with Monte Carlo Simulation to study the impact of prolonged or continuous infusion therapy in order to predict clinical response rates. Administration of piperacillin-tazobactam by 4 h infusion (prolonged infusion) resulted in a greater proportion of patients reaching the $fT > MIC$ target of 50% compared to conventional dosing if the MIC was in the range 4–16 mg/L [18–21]. Similar results have been reported for meropenem administered as 1 g over 3 h compared to conventional dosing. The proportion of patients who reached the $fT > MIC$ target is increased to a clinically meaningful level (>90%) if the MIC is in the range 2–4 mg/L. Use of 2 g meropenem infusion over 3–4 h or continuous infusion of 6 g/day would increase this to 2–8 mg/L [22,23]. Doripenem has been studied in clinical trials of hospital acquired pneumonia at a dose of 500 mg 8 h by 4 h infusion. Using $fT > MIC$ target of 40–50% the 4 h infusion resulted in a clinically meaningful proportion of the modelled population reaching the pharmacodynamic target for strains in the MIC range 2–4 mg/L [24]. Similar data on prolonged infusion ceftazidime or cefepime are available [25,26].

Using piperacillin tazobactam as an example, the MIC range where prolonged or continuous infusion therapy is likely to have a beneficial impact is illustrated on Table 4. The pathogens were isolated in the UK in 2009–2010 from respiratory secretions of hospitalised patients with pulmonary infection or those with blood stream infection [27]. Prolonged or continuous infusion is most likely to be of benefit as therapy in those patients infected with strains in the range 8–16 mg/L hence for *P. aeruginosa* infection 18–36% of strains have MICs that may show benefit. By contrast, for *E. coli* or *Enterobacter cloacae* only 7.5–10% of strains fall within this range, hence the impact of continuous or prolonged infusion therapy on outcomes is likely to be much more modest. Selection of piperacillin-tazobactam dosing methods for aerobic Gram-negative bacillary infection by MIC determination is one way of identifying the subgroup of patients in whom prolonged or continuous infusion therapy will be of most benefit. However, this places significant emphasis on a laboratory measure that can be variable.

Table 5 illustrates some possible therapeutic breakpoints for four Beta-lactams if given by continuous or prolonged

Table 5

Comparison of EUCAST clinical breakpoints for standard dosing of piperacillin-tazobactam, meropenem, doripenem and ceftazidine compared to the same daily doses given by continuous or prolonged infusion

	Clinical breakpoint (mg/L)		Breakpoint for prolonged/continuous infusion (mg/L)
	Enterobacteriaceae	<i>P. aeruginosa</i>	
Ceftazidine	≤1	≤8	≤16
Doripenem	≤1	≤1	≤4
Meropenem	≤2	≤2	≤8
Piperacillin-tazobactam	≤8	≤16	≤16

infusion therapy in comparison to those already recommended by EUCAST for intermittent dosing.

Human clinical studies

Prolonged or continuous infusion therapy has been investigated in a range of comparative trials with conventional intermittent injection using different penicillins, cephalosporins and the carbapenem, meropenem. A range of different Gram-positive and Gram-negative pathogens have been targeted as well as use an empiric and definitive therapy in a range of healthcare settings. It remains unclear which particular patient groups benefit most from prolonged or continuous infusion therapy but our existing data suggest patients infected pathogens with elevated MICs (2–4 fold above existing EUCAST clinical breakpoints), patients with altered patho-physiology and those with more severe infection are most likely to benefit most. However, a systematic review of continuous infusion Beta-lactams involving fourteen randomised controlled trials and 846 patients indicated continuous infusion did not improve clinical cure ($n = 755$, odds ratio 1.10, 95% confidence intervals 0.74–1.46) or mortality ($n = 541$, odds ratio 1.0, 95% confidence interval 0.48–2.06) [28^{••}]. Hence, patient selection for prolonged or continuous infusion remains central to its use in clinical practice as well as the construction of clinical trials designed to show benefit. So far, few published studies in man have adequately studied the risk of emergence of resistance comparing prolonged or continuous infusion to standard therapy.

Penicillins

Piperacillin-tazobactam has been studied in a number of comparative trials comparing prolonged or continuous infusion to conventional dosing. Continuous infusion was compared to intermittent infusion in a group of 98 patients with mainly skin and skin structure, respiratory or intra abdominal infection and found to be superior in terms of microbiological success, more rapid resolution of fever and reduced costs. Clinical cure rates were not changed [29]. A much larger prospective randomised trial in complicated intra-abdominal infection ($n = 262$) indicated no differences in clinical cure, microbiological success, resolution of fever or peripheral white blood cell count in the continuous infusion group compared to intermittent injection [30]. Prolonged infusion piperacillin-tazobactam (4 h infusion time) was compared to intermittent infusion in a group of 194 patients with documented *P. aeruginosa* infection. In those patients with APACHE II scores of ≥ 17 ($n = 79$) prolonged infusion therapy reduced mortality and shortened length of stay ($p < 0.05$). For the majority of patients ($n = 115$) who had APACHE scores of < 17 mortality and length of stay were unaltered [19]. Unfortunately, in this study, MIC values of the *P. aeruginosa* strains were not available and serum concentrations of drug were not determined. However, in a different

Table 6

Comparison of clinical cures with continuous infusion or intermittent dosing piperacillin-tazobactam in VAP [31[•]]

	Continuous infusion ($n = 27$)	Intermittent infusion ($n = 46$)	<i>p</i> value
Cure (%)	33/37 (89)	26/46 (56)	0.001
Cure			
MIC 4 mg/L	18/20 (90)	19/25 (76)	0.20
MIC 8 mg/L	8/9 (89)	6/15 (40)	0.02
MIC 16 mg/L	7/8 (88)	1/6 (17)	0.02

study of continuous infusion piperacillin-tazobactam compared to standard dosing in patients with ventilator associated pneumonia (VAP) due to Gram-negative bacilli (mainly Enterobacteriaceae or *P. aeruginosa*) a difference in clinical cure could be related to MIC value (Table 6) [31[•]].

Finally, a large retrospective study of 107 patients compared those who received continuous infusion oxacillin to conventional dosing for MSSA infective endocarditis 30 day mortality and length of stay were similar between the two groups but microbiological cure was superior with continuous infusion [32].

Cephalosporins

The pharmacodynamics of cefepime was studied in 29 patients with documented Gram-negative bacillary infection. $T > MIC$ was related to outcome with a microbiological success rate of 89% if the $T > MIC$ was 100% and a cure rate of 0% if the $T > MIC$ was $< 100\%$ [33]. More recently the rate of clinical cure with ceftobiprole in skin and skin structure infection was related to a $fT > MIC$ value of $\geq 30\%$ or $\geq 50\%$ [34^{••}].

Twenty years ago Lagast *et al.* [35] compared continuous infusion cefoperazone to intermittent injection in 45 patients with Gram-negative septicaemia. No difference in clinical response was observed. Similar data were reported for ceftazidime in acute exacerbation of severe chronic bronchitis where continuous infusion therapy was as effective as intermittent injections in terms of clinical and bacteriological outcomes in a cohort of 81 patients [36]. In a retrospective analysis of continuous versus intermittent infusion ceftazidime in VAP, continuous infusion therapy was associated a higher rate of clinical cure (50/56 (89%)) vs 34/65 (52%) OR 12.2 98% CI 3.5–43.2, $p < 0.001$). However, no association was found between the type of ceftazidime infusion, the MIC of the pathogen and clinical outcome [37]. A multi-centre prospective randomised cross-over study comparing continuous infusion to intermittent injection ceftazidime in patients with cystic fibrosis recruited 69 patients [38[•]]. Improvement in FEV₁, was taken as the end point and showed no differences between the two

groups except for patients from whom resistant (MIC > 32 mg/L) pathogens were isolated when FEV₁ was better with continuous infusion. The interval between repeat courses of antibiotics was longer with continuous infusion and patients preference was greater. There was no difference in isolation of resistance organisms [38•].

Continuous infusion ceftriaxone, cefuroxime and cephamandole have also been studied in clinical trials. In a prospective open label randomised study of 57 patients with clinically diagnosed sepsis showed no difference in clinical response, or bacteriological responses comparing continuous versus intermittent infusion ceftriaxone. However, a logistic regression analysis indicated continuous infusion was associated with improved outcomes when age and severity of sepsis were controlled for [39]. A prospective randomised study comparing continuous infusion to intermittent injection cefamandole to treat febrile episodes in cancer patients the continuous infusion group was equivalent over all to intermittent injection. However, improved responses were observed in those with microbiologically confirmed Gram-negative bacillary infection and those with persistent neutropenia [40].

Finally, a cohort study comparing continuous infusion cefuroxime to bolus injection in a range of infections – mainly pulmonary indicated lower doses of cefuroxime were used and length of treatment and hospital stay were shortened and financial savings were made [41].

Carbapenems

A number of studies have reported meropenem pharmacokinetic and pharmacodynamic properties when administered by continuous or prolonged infusion. However, there is very little clinical experience reported from randomised controlled trials [42]. Lorrente *et al.* [43], performed a retrospective cohort study in patients with VAP caused by Gram-negative bacilli who were treated with meropenem by continuous infusion or intermittent injection showing cure rates were higher in those receiving continuous infusion (38/42

(90.5%) vs 28/47 (59.6%), odds ratio 6.4 (95% confidence limits 2.0–21.0, $p < 0.001$). Responses were not stratified by MIC.

Risk of emergence of resistance

Clinical pharmacodynamic studies on the impact of Beta-lactam dosing and risk of resistance are scarce. It is known that low dose prolonged treatment oral B. lactams favour the carriage of penicillin resistant *Streptococcus pneumoniae* in children [44]. In addition, in a randomised trial short course, high dose amoxicillin reduced the carriage of penicillin resistant *S. pneumoniae* compared to low dose, long duration [45]. Data comparing prolonged or continuous infusion therapy Beta-lactam to conventional dosing are lacking, however, continuous infusion ceftazidime did not seem to increase the proportion of resistant *P. aeruginosa* in cystic fibrosis patients [38•].

Conclusions

Pre-clinical and human population pharmacokinetic data, combined with Monte Carlo Simulation, would predict that continuous or prolonged infusion Beta-lactams would have clinical benefit. However, the results of clinical trials comparing these modes of administration to intermittent injection most often fail to demonstrate superiority in microbiological or clinical end points. This is most probably because such trials fail to enrich for the patients most likely to see benefit and also fail to control for pharmacokinetic variability. The patients most likely to benefit are those infected with pathogens with MIC values at, or 2–4 fold higher, than the existing EUCAST clinical breakpoints (Table 5). In addition, therapeutic drug monitoring of B. lactams with dose individualisation to achieve pre-defined T > MIC targets may improve clinical outcomes, reduce risks of resistance and produce health economic improvements [46•]. At present, the clinical data do not support the widespread use of continuous or prolonged infusion B. lactam therapy and it is unlikely to have a significant impact on meeting the challenges of increasing Gram-negative resistance as, at best, it will allow treatment of borderline or low level resistance.

Table 7

Unresolved issues for continuous or prolonged infusion Beta-lactam therapy

- What is the optimal fT > MIC target to employ in man – some evidence suggests this needs to be higher than static effect targets in pre-clinical models.
- Is dose individualisation based on measurement Beta-lactam serum concentrations merited – little data in this area at present
- Which pathogen MICs are most optimally treated with prolonged or continuous infusion therapies – clinical trials required to validate predictions from population pharmacokinetics and Monte Carlo Simulation
- Which patient groups in which healthcare settings are most likely to benefit – clinical trials required in severe sepsis and patients with multiple comorbidities
- How continuous or prolonged infusion therapy impacts on the risk of emergence of resistance in the targeted pathogens – clinical trials required as little data at present.

The unresolved issues in continuous or prolonged B. lactam therapy are listed on Table 7.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Roberts JA, Paratz J, Paratz E, Krueger WA, Lipman J:
•• **Continuous infusion of B. lactam antibiotics in severe infections: a review of its role.** *Int J Antimicrob Agents* 2007, **30**:11-18.
- An up-to-date review of the pharmacokinetic, clinical and health economic advantages of continuous infusion therapy in severe infection.
2. Lotholary O, Lefort A, Tod M, Charnot A-M, Darras-Jolly C, Cordonnier C: **Pharmacodynamic and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia.** *Lancet Infect Dis* 2008, **8**:612-620.
3. Mouton JW, Ambrose PG, Canton R, Drusano GL, Harbarth S,
•• MacGowan A, Theuretzbacher U, Turnidge J: **Conserving antibiotics for the future: new ways to use old and new drugs from the pharmacokinetic and pharmacodynamic perspective.** *Drug Resist Updat* 2011 doi: 10.1016/J.drup.2011.02.005.
- An up-to-date statement of the role of pharmacokinetics and dynamics in preserving new and old therapies. Includes suggested research priorities.
4. McNabb JJ, Bui KQ: In *B. lactam Pharmacodynamics in Antimicrobial Pharmacodynamics in Theory and Clinical Practice*. Edited by Nightingale CH, Murakawa T, Ambrose PG. Basel: Marcell Dekker; 2002:99-124.
5. Hyatt JM, Nix DE, Stratton CW, Schjertag JJ: **In vitro pharmacodynamics of piperacillin, piperacillin-tazobactam, and ciprofloxacin alone and in combination against Staphylococcus aureus, Klebsiella pneumoniae, Enterobacter cloacae and Pseudomonas aeruginosa.** *Antimicrob Agents Chemother* 1995, **39**:1711-1716.
6. Bowker KE, Holt HA, Reeves DS, MacGowan AP: **Bactericidal activity, post antibiotic effect and modified controlled effective regrowth time of meropenem at high concentrations.** *J Antimicrob Chemother* 1996, **38**:1055-1060.
7. Periti P, Nicoletti P: **Classification of B. lactam antibiotics according to their pharmacodynamics.** *J Chemother* 1999, **11**:323-330.
8. Vogelmann BS, Craig WA: **Post antibiotic effects.** *J Antimicrob Chemother* 1985, **15**(Suppl. 1):37-46.
- An excellent review of this topic that has now fallen out of favour and is rarely critically discussed.
9. Leggett JE, Fantin B, Ebert S, Totsuka K, Vogelmann B, Calame W, Mattie H, Craig WA: **Comparative antibiotic dose-effect relationships at several dosing intervals in murine pneumonia and thigh infection models.** *J Infect Dis* 1989, **159**:281-292.
10. Bakker-Woudenberg IAJM, Kate MT, Goessens WHF, Mouton JW:
• **Effect of treatment duration on pharmacokinetic-pharmacodynamic indices correlating with therapeutic efficacy of ceftazidime in experimental Klebsiella pneumoniae lung infection.** *Antimicrob Agents Chemother* 2006, **50**:2919-2925.
- This interesting work challenges our existing pre-conceptions of B. lactam pharmacodynamics comparing the pharmacodynamic drives in short versus long duration therapy.
11. Alou L, Aguilar L, Sevillano D, Gimenez MJ, Echeverria O, Gomez-Lus ML, Prieto J: **Is there a pharmacodynamic need for the use of continuous versus intermittent infusion with ceftazidime against Pseudomonas aeruginosa: an in vitro pharmacodynamic model.** *J Antimicrob Chemother* 2005, **55**:209-213.
12. Kim A, Banevivius MA, Nicolau DP: **In vivo pharmacodynamic profiling of doripenem against Pseudomonas aeruginosa by stimulating human exposures.** *Antimicrob Agents Chemother* 2008, **52**:2497-2502.
13. Bulik CC, Christensen H, Li P, Sutherland CA, Nicolau DP, Kuti JL: **Comparison of the activity of a human simulated, high dose, prolonged infusion of meropenem against Klebsiella pneumoniae producing the KPC carbapenemase versus that against Pseudomonas aeruginosa in an in vitro pharmacodynamic model.** *Antimicrob Agents Chemother* 2010, **54**:804-810.
14. Stearne LET, Goessens WHF, Mouton JW, Gyssens IC: **Effect of dosing and dosing frequency on the efficacy of ceftizoxime and emergence of ceftizoxime resistance during early development of murine abscesses caused by Bacteroides fragilis and Enterobacter cloacae mixed infection.** *Antimicrob Agents Chemother* 2007, **51**:3605-3611.
15. MacGowan AP, Noel AR, Tomaselli S, Elliott H, Bowker KE: **Pharmacodynamics of the antibacterial effect and emergence of resistance to razupenem (PZ601) in an in vitro pharmacokinetic model of infection.** *Antimicrob Agents Chemother* 2011, **55**:1436-1440.
16. Tam VH, Schilling AN, Neshat S, Poole K, Melnick DA, Coyle EA: **Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance in Pseudomonas aeruginosa.** *Antimicrob Agents Chemother* 2005, **49**:4920-4927.
17. Kasiakou SK, Lawrence KR, Choulis N, Falagas ME: **Continuous**
•• **versus intermittent intravenous administration of antibacterials with time-dependent action: a systemic review of pharmacokinetic and pharmacodynamic parameters.** *Drugs* 2005, **65**:2499-2511.
- A systemic review of all published Current Contents and Cochrane register relevant articles up to Jan 2005.
18. Lodise TP, Lomaestro B, Rodvold KA, Danziger LH, Drusano GL: **Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo Simulation.** *Antimicrob Agents Chemother* 2004, **48**:4718-4724.
19. Lodise TP, Lomaestro B, Drusano GL: **Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of extended infusion dosing strategy.** *Clin Infect Dis* 2007, **44**:357-363.
20. Roberts JA, Kirkpatrick CMJ, Roberts MS, Dalley AJ, Lipman J: **First dose and steady state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis.** *Int J Antimicrob Agents* 2010, **35**:156-163.
21. Patel N, Scheetz MH, Drusano GL, Lodise TP: **Identification of Optimal Renal Dosage adjustments for traditional and extended infusion piperacillin-tazobactam dosing regimens in hospitalized patients.** *Antimicrob Agents Chemother* 2010, **54**:460-465.
22. Nicolau DP: **Pharmacokinetic and pharmacodynamic properties of meropenem.** *Clin Infect Dis* 2008, **47**:532-540.
23. Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J: **Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution.** *J Antimicrob Chemother* 2009, **64**:142-150.
24. Bhavnani S, Hammel JP, Cirincione B, Wikler MA, Ambrose PG: **Use of pharmacokinetic/pharmacodynamic target attainment analysis to support Phase 2 and 3 dosing strategies for doripenem.** *Antimicrob Agents Chemother* 2005, **49**:3944-3947.
25. Kim A, Kuti JL, Nicolau DP: **Probability of pharmacodynamic target attainment with standard and prolonged infusion antibiotic regimens for empiric therapy in adults with hospital-acquired pneumonia.** *Clin Pharm* 2009, **31**:2765-2778.
26. Roos JF, Bulitta J, Lipman J, Kirkpatrick CMJ: **Pharmacokinetic-pharmacodynamic rationale for cefipime dosing regimens in intensive care units.** *J Antimicrob Chemother* 2006, **58**:987-993.
27. www.bsacsurv.org accessed June 2011.

28. Roberts JA, Webb SS, Paterson D, Hok M, Lipman J: **A systematic review on the clinical benefits of continuous administration of B. lactam antibiotics.** *Crit Care Med* 2009, **37**:2071-2078.
A meta analysis of prospective randomised controlled trials conducted up to November 2007.
29. Grant EM, Kuti JL, Nicolau DP, Nightingale C, Quintiliani R: **Clinical efficacy and pharmco-economics of a continuous infusion piperacillin-tazobactam programme in a large community teaching hospital.** *Pharmacotherapy* 2002, **22**:471-483.
30. Lau WK, Mercer D, Hanik, Nicolau DP, Kuti JL, Mansfield D, Dana A: **Randomised open label comparative study of piperacillin-tazobactam administered by continuous infusion versus intermittent infusion for treatment of hospitalized patients with complicated intra-abdominal infection.** *Antimicrob Agents Chemother* 2006, **50**:3556-3561.
31. Lorente L, Jimenez A, Martin MM, Iribarren JL, Jimenez JJ, Mora ML: **Clinical cure of ventilator-associated pneumonia treated with piperacillin-tazobactam administered by continuous or intermittent infusion.** *Int J Antimicrob Agents* 2009, **33**:464-468.
One of the few papers to show superiority of continuous infusion therapy outside a subgroup analysis. Improved responses apparent in the strains with MICs of 8–16 mg/L as expected.
32. Hughes DW, Frei CR, Maxwell PR, Green K, Patterson JE, Crawford GE, Lewis JS: **Continuous versus intermittent infusion of oxacillin for treatment of infective endocarditis caused by methicillin susceptible Staphylococcus aureus.** *Antimicrob Agents Chemother* 2009, **53**:2014-2019.
33. Tam VH, McKinnon PS, Akins RL, Rybak MJ, Drusano GL: **Pharmacodynamics of cefepime in patients with Gram-negative infections.** *J Antimicrob Chemother* 2002, **50**:425-428.
34. Kimko H, Xu X, Nandy P, Samtani M, Strauss RS, Bagchi P, Noel GJ: **Pharmacodynamic profiling of ceftobiprole for the treatment of complicated skin and skin structure infections.** *Antimicrob Agents Chemother* 2009, **53**:3371-3374.
One of the few clinical papers to convincingly relate $ft > MIC$ to clinical outcomes in man.
35. Lagast H, Meunier-Carpentier F, Klastersky J: **Treatment of Gram-negative bacillary septicemia with cefoperazone.** *Eur J Clin Microbiol* 1983, **2**:554-558.
36. Lubasch A, Luck S, Lode H, Mauch H, Lorenz J, Bolcskei P, Welte T: **Optimizing ceftazidime pharmacodynamics in patients with acute exacerbation of severe chronic bronchitis.** *J Antimicrob Chemother* 2003, **51**:659-664.
37. Lorente L, Jimenez A, Palmero S, Jimenez JJ, Iribarren JL, Santana M, Martin MM, Mora ML: **Comparison of clinical cure rates in adults with ventilator associated pneumonia treated with intravenous ceftazidime administered by continuous or intermittent infusion: a retrospective open label, historical chart view.** *Clin Ther* 2007, **29**:2433-2439.
38. Hubert D, Le Roux E, Lavrut T, Wallaert B, Scheid P, Manach D, Grenet D, Sermet-Gaudelus I, Ramel S, Cracowski C et al.: **Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis.** *Antimicrob Agents Chemother* 2009, **53**:3650-3656.
This well designed prospective multi-centre cross-over study showed no difference in continuous infusion versus intermittent injection ceftazidime except in a subgroup analysis of patient with resistant organisms. Quality of life scores were similar but most patients preferred continuous infusion.
39. Roberts JA, Boots R, Rickard CM, Thomas P, Quinn J, Roberts DM, Richards B, Lipman J: **Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomised controlled pilot study.** *J Antimicrob Chemother* 2007, **59**:285-291.
40. Bodey GP, Ketchel SJ, Rodriguez V: **A randomised study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients.** *Am J Med* 1979, **67**:608-616.
41. Zeisler JA, McCarthy JD, Richelieu WA, Nichol MB: **Cefuroxime by continuous infusion: a new standard of care?** *Infect Med* 1992, **9**:54-60.
42. Perrott J, Mabasa VH, Ensom MHH: **Comparing outcomes of meropenem administration strategies based on pharmacokinetic and pharmacodynamic principles: a qualitative systematic review.** *Ann Pharmacother* 2010, **44**:557-564.
43. Lorente L, Lorenzo L, Martin MM, Jimenez A, Mora ML: **Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to Gram-negative bacilli.** *Ann Pharmacother* 2006, **40**:219-223.
44. Guillemot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervodan F, Bouvenot G, Eschwege E: **Low dosage and long treatment duration of B. lactam: risk factors for carriage of penicillin resistant Streptococcus pneumoniae.** *JAMA* 1998, **279**:365-370.
45. Schrag SJ, Pena C, Fernandez J, Sanchez J, Gomez V, Perez E, Feris J, Besser RE: **Effect of short course, high dose amoxicillin therapy on resistant pneumococcal carriage.** *JAMA* 2001, **286**:49-55.
46. Roberts JA, Uldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J: **Therapeutic drug monitoring of B. lactams in critically ill patients: proof of concept.** *Int J Antimicrob Agents* 2010, **36**:332-339.
This is the first report of the use of therapeutic drug monitoring to achieve pre-defined pharmacodynamic targets.