AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Continuous and Prolonged Intravenous β-Lactam Dosing: Implications for the Clinical Laboratory

Mordechai Grupper, Joseph L. Kuti, David P. Nicolau

Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, USA

SUMMARY

Beta-lactam antibiotics serve as a cornerstone in the management of bacterial infections because of their wide spectrum of activity and low toxicity. Since resistance rates among bacteria are continuously on the rise and the pipeline for new antibiotics does not meet this trend, an optimization of current beta-lactam treatment is needed. This review provides an overview of optimization through use of prolonged- and continuous-infusion dosing strategies compared with more traditional intermittent infusions. Included is an overview of the scientific basis for using these nontraditional prolonged- and continuous-infusion-based regimens, with a focus on major areas in which the clinical laboratory can support the clinical use of these regimens.

INTRODUCTION

The advent of antibiotics in the 1930s resulted in a tremendous positive impact on the treatment of the most common bacterial infectious diseases. Despite the countless benefits of antibiotics observed over the decades, the effectiveness of these life-saving drugs has been diminished by resistance, and in some scenarios the net effect is a return to the preantibiotic era (1–3). Indeed, antimicrobial resistance remains a global health issue as stated by the World Health Organization (2). The Infectious Diseases of America (IDSA) also describes a number of bacterial pathogens that are among the most concerning from a resistance standpoint. IDSA lists *Staphylococcus aureus*, *Enterococcus* species, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* as bacterial pathogens that continually evade current antimicrobial activity (3). Alarming rates of resistance are seen, for example, in *Klebsiella* species, with some countries reporting resistance to third-generation cephalosporins in more than 60% of isolates and resistance to carbapenems in greater than 50% of isolates (2). In many countries, methicillin resistance (i.e., causing resistance to most beta-lactam antibiotics as well as other antibiotic classes) is observed in 20% to 80% of *S. aureus* isolates (2).

The continual threat of these resistant bacteria is unmet by our current antibiotic armamentarium because new drugs are not being developed at the necessary pace (1–3). Therefore, innovative strategies that improve the "effectiveness" of currently available antibiotics are essential. Employing pharmacokinetic/pharmacodynamic (PK/PD) principles during design of dosing regimens for various available antimicrobials could be an effective way to improve the current situation (4). While exposure optimization (i.e., PD profiling) is already an established field of study, it has not been fully exploited, as these technologies are not universally used in the hospital setting. Available data suggest that for certain antibiotics, PD can be utilized to augment efficacy by manipulating the duration of the intravenous infusion (4–9). Beta-lactam antibiotics are highly appealing for such a strategy. These agents are among the most commonly used in various health care settings, have been thoroughly investigated, and are well worth preserving as a viable treatment option due to their broad-spectrum activity and excellent tolerability (7).

Although our understanding regarding beta-lactam PK/PD optimization has substantially broadened, we still face major challenges in implementation of dosing based on these strategies. First, in order to optimize therapy, we must understand the target or "therapeutic" concentration to aim for. Since beta-lactam concentrations are typically referenced to the MIC of the drug needed to inhibit bacteria, understanding the precise MIC, and in some scenarios the genotypic presence of resistance mechanisms, for each beta-lactam will be paramount (10). Once a target threshold

Published 13 July 2016

Citation Grupper M, Kuti JL, Nicolau DP. 2016. Continuous and prolonged intravenous β-lactam dosing: implications for the clinical laboratory. Clin Microbiol Rev 29:759–772. doi:10.1128/CMR.00022-16.

Address correspondence to David P. Nicolau, david.nicolau@hhchealth.org.

and MIC are established, some confidence in the patient's specific pharmacokinetic profile is required to design an optimal and targeted dose (11). Unlike the case for vancomycin and some aminoglycosides, however, the availability of assays to clinically test for beta-lactam concentrations is limited. As a result, the clinical laboratory plays a prominent and ever-growing part in institutional antimicrobial stewardship (12) and therefore can offer solutions for overcoming the above challenges.

This review will briefly introduce the concept of prolonged- and continuous-infusion beta-lactam dosing and then discuss the emerging opportunities for the clinical laboratory in achieving the goal of individualized antibiotic therapy. In addition, practical examples of optimizing beta-lactam dosing by way of nontraditional infusions will be provided.

BETA-LACTAM PHARMACODYNAMICS

A comprehensive review of beta-lactam pharmacodynamics can be found in historical publications (13). Briefly, beta-lactam antibiotics display concentration-independent, commonly referred to as time-dependent, killing of bacteria. This means that once a critical concentration is obtained, no further speed or extent of killing is observed with increasing concentrations and that the time that free drug concentrations remain above the MIC ($fT>$MIC) becomes a better predictor of killing. The goal of therapy, therefore, is to maximize the $fT>$MIC as a percentage of the dosing interval. For each beta-lactam class, the percent $fT>$MIC needed for maximizing efficacy is different. Maximal bacterial killing for the penicillins, cephalosporins, carbapenems, and monobactams, for example, occurs when the $fT>$MIC is approximately 50 to 60%, 60 to 70% (14), 40% (15), and 50 to 60% of the dosing interval, respectively (14). This is in contrast with concentration-dependent antibiotics, including fluoroquinolones and aminoglycosides, which exert maximal bacterial killing when their peak concentration or area under the concentration-time curve in a dosing period is maximized relative to the MIC (10). When given intravenously, beta-lactams can be administered by three basic strategies. The most prevalent is the traditional intermittent schedule, which involves infusion of each fraction of the daily dosage over a short time intervals, i.e., 5 to 60 min. When each fraction of the daily dosage is infused over three or more hours, this dosing strategy is referred to as a prolonged or extended infusion. Of note, the terms prolonged and extended are used alternately in the literature but are interchangeable. Finally, when all of the drug daily dosage is administered without any interruption over a dosing interval, the schedule is referred to as a continuous infusion (7, 13–19). At certain MICs, prolonged and continuous infusion schedules increase the $T>$MIC more than would otherwise occur with a short intermittent infusion schedule (Fig. 1). Additionally, a prolongation of the dosing interval would be especially beneficial when using agents with a short half-life, a characteristic typical of many beta-lactam agents (13–19).

HISTORICAL REVIEW

It is of interest to briefly review the nonclinical studies that formed the basis for the current understanding of prolonged and continuous dosing of antibiotics. Over 65 years ago, studies by Eagle and coworkers and Schmidt and coworkers in various animal models of streptococcal infection demonstrated that frequent or continuous dosing of penicillin G achieved a more rapid cure of the infected animal than infrequent (i.e., once or twice daily) dosing

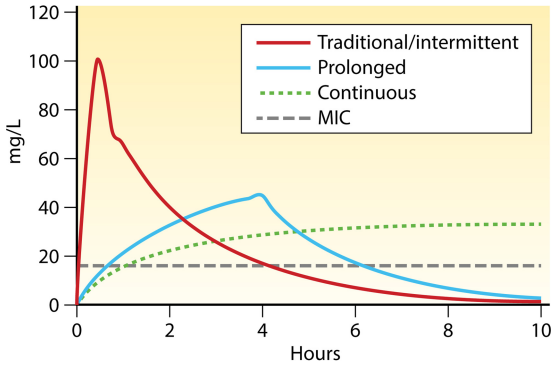


FIG 1 Schematic plot demonstrating the effects of prolonged and continuous beta-lactam infusion dosing regimens on the concentration-time curve and time above an MIC, compared with traditional intermittent infusion.

(20–22). Later studies pointed out the superior effect of continuous infusion of penicillin G in models that used animals that were either immunosuppressed or venom treated (23, 24). Animal and *in vitro* studies conducted during the 1980s and early 1990s have particularly emphasized the consistently greater efficacy of continuous infusion or more frequent dosing of beta-lactams against Gram-negative bacteria. Although this supported the potential advantage of using continuous and prolonged infusions, the clear superiority of these methods over intermittent dosing had yet to be demonstrated (25–37).

Many clinical studies assessing continuous and prolonged infusion were conducted through the 1990s, but only a few were clinical randomized controlled trials, mostly addressing only pharmacologic endpoints (38–49), and only two reported patients' outcomes. In 1979, Bodey and colleagues found that an antibiotic combination containing continuous-infusion cefamandole achieved the greatest cure rates in 490 febrile episodes with neutropenia (48). In contrast, Lagast and colleagues observed no statistical difference regarding outcome in favor of continuous cefoperazone in 45 patients with Gram-negative sepsis (49).

Although the scientific rationale and the proof of concept seem evident given data that accumulated from the development of penicillin through the 1990s, the lack of supportive solid clinical evidence and major practical issues delayed the incorporation of nontraditional infusions into common clinical practice. Indeed, prolonged or continuous infusion may reduce patient mobility, demands prolonged and secured intravenous access, and requires special equipment, including infusion pumps and sets. These methods also demand a higher level of training and are more labor-intensive. Possible instability and degradation of the antibiotic at room temperature, as exemplified by the carbapenems, should also be considered, particularly with the case of the continuous-infusion strategy (50, 51).

CONTEMPORARY STUDIES

In sharp contrast to the above description, numerous nonclinical experiments, clinical studies, and meta-analyses have been conducted over the last 15 years in the area of nontraditional beta-lactam dosing. A significant contribution to the field was the introduction of advanced PD analyses of data collected from *in vitro*, animal, and human studies, which also diminishes the need for expensive, complicated clinical trials. The latter study methodology is conducted by computerized simulations that use probabil-

ity models. The best-known and most widely used method is the Monte Carlo simulation (52). This simulation experiment, when applied for antimicrobial treatment considerations, requires as its input only the pharmacokinetic parameter estimates and their variability from a sample target population who have previously received the antibiotic. The software can then simulate a population of thousands of virtual patients based on this input and the provision of a compartmental model. The results of the former step serve in turn for determining the probability of a specific dosing regimen achieving the target PD exposure in the population, for instance, a defined *fT*>MIC at a given MIC dilution. This likelihood is referred as to the probability of target attainment (PTA) (16, 52, 53). Recent Monte Carlo simulation examples include selection of a prolonged infusion of doripenem (500 mg as a 4-h infusion every 8 h [q8h]) to be investigated in a hospital-acquired pneumonia clinical trial (52, 53), a PD analysis of critically ill patients that showed increased piperacillin-tazobactam and meropenem exposure using extended, 3-h infusions compared with 30-min intermittent infusions (16), and a study demonstrating that 4-h extended infusions of piperacillin-tazobactam doses equal to or greater than 3.375 g q8h achieved superior PTA at an MIC equal to 16 μg/ml (54). Additional Monte Carlo simulation examples can be found in a thorough review by George and colleagues (55). Although not sufficient to replace clinical trials, Monte Carlo simulations can provide important decision support for which drug regimens are going to provide the greatest likelihood of success during clinical studies. The results of such analyses are often also used to guide clinical practice, when clinical studies are not yet available or impractical (56).

Unfortunately, contemporary clinical comparative trials conducted in the last decade do not provide clear guidance regarding whether a traditional intermittent schedule or a continuous/extended infusion schedule is more beneficial for all patients (53, 57–87). Abdul-Aziz and colleagues (88) published a rigorous analysis of the clinical evidence and concluded that it was not sufficient for a change in dosing regimens toward nontraditional infusions of beta-lactams. Nonetheless, they included an in-depth discussion of the limitations of the studies conducted until the time of their publication; the vast majority of studies were found to suffer from considerable limitations, precluding the interpretation of their results. Noteworthy are the inclusion in the analysis of studies of antibiotics other than beta-lactams, nonoptimally designed trials, comparison of different dosages in the different arms of randomized controlled trials, low-MIC pathogens (so that even the traditional dosing regimen achieved adequate *fT*>MIC), and highly heterogeneous patient populations.

It is notable, however, that no clinical study has ever demonstrated inferiority of a prolonged- or continuous-infusion drug regimen to the same antibiotic given as a traditional infusion. Nevertheless, a closer look at studies that have focused on the more selective patient populations can be instructive. Lodise et al. (69) conducted a retrospective investigation of piperacillin-tazobactam as an extended 4-h infusion for treating documented *P. aeruginosa* infections. The 4-h prolonged-infusion regimen was administered to 102 patients, and these were compared with a recent historical cohort who received an intermittent (i.e., traditional) infusion ($n = 92$ patients). For patients with acute physiology and chronic health evaluation II (APACHE II) scores of ≥17, the 14-day mortality rate was significantly lower when the extended schedule was used than with the intermittent one, but mortality was similar for the dosing strategies in the less sick patients. A later retrospective study by Bauer et al. (77), including patients with documented *P. aeruginosa* pneumonia or bacteremia treated with extended or intermittent infusions of cefepime, also observed a significantly lower mortality rate among those who received the extended infusion (3% versus 20%; $P = 0.03$). Importantly, the regimen design of these two studies utilized Monte Carlo simulation to guide selection of their optimized dosing regimens based on the *P. aeruginosa* strains most prevalent in their hospitals, meaning that the regimens were targeted at the institutions' specific isolate MIC distribution. An open-label, randomized trial by Roberts and colleagues (58) enrolled 57 patients with sepsis hospitalized in the intensive care unit (ICU). Patients received ceftriaxone at 2 g either as an intermittent infusion once daily or as a 24-h continuous infusion. This study, one of the few to have adequate allocation and masking, found a significantly improved outcome in the subgroup of patients who received continuous-infusion ceftriaxone for 4 days or more. Collectively, these studies thus represent populations with serious but not moribund disease and therefore more dependent on the efficacy of antibiotic. In further support of these observations, Lee and colleagues (73) reported results of a retrospective study from 2 intensive care units addressing pre- and postimplementation of a prolonged-infusion piperacillin-tazobactam regimen. One hundred forty-eight patients were included; 80 received a traditional intermittent-infusion regimen, and 68 received a prolonged-infusion regimen. The majority of included patients had pneumonia, sepsis, or both. The investigators observed that patients receiving prolonged infusion had significantly lower 30-day mortality (19%) than patients receiving traditional dosing regimens (38%, $P = 0.01$).

The most rigorously designed clinical studies to comparatively investigate different beta-lactam dosing schedules are probably the two known as BLING (beta-lactam infusion group) I and BLING II (86, 87), both multicenter, prospective, double-blind, randomized controlled trials. The former enrolled 60 patients, all with severe early sepsis, allocated evenly between an intervention arm (continuous infusions of piperacillin-tazobactam, meropenem, or ticarcillin-clavulanate) and a control arm (the same drugs administered on an intermittent schedule). Clinical cure in the intervention group was 70% and significantly exceeded that in the control group (43%) ($P = 0.037$); furthermore, survival to hospital discharge was greater (90% versus 80%) in the intervention group, although this was not statistically significant. BLING II had the same methodology as the first trial but enrolled 432 patients from 25 intensive care units across Australia, Asia, and Europe. In contrast to BLING I, the larger study did not find a difference in the primary endpoint of alive, intensive care unit-free days at day 28, a unique endpoint relative to other studies of continuous or prolonged infusion. Nevertheless, the authors acknowledged some major limitations of BLING II, including possible predominance of low-resistance pathogens, and that the study was not powered for the detection of mortality differences between the groups. An even larger study, targeting more resistant bacteria, is planned. Notably, the BLING studies did not define optimized continuous or prolonged beta-lactam dosing regimens that targeted the bacteria at each participating site (unlike the single-center studies described above), which may have also contributed to a lack of difference. Tables 1 and 2 summarize the findings of the main clinical studies comparing prolonged- and

TABLE 1 Summary of main clinical studies comparing continuous infusion with intermittent infusion of beta-lactams[a]

Reference	Study design	No. of patients/illness	Microbiological findings	Dosing regimen	Major endpoint findings
Hanes et al., 2000 (67)	RCT	32/nosocomial pneumonia	GNB	CAZ 60 mg/kg/day CI vs CAZ 2 g q8h II	No difference in treatment outcomes
Nicolau et al., 2001 (66)	RCT	35/nosocomial pneumonia	GPB + GNB	CAZ 3 g/day CI vs CAZ 2 g q8h II	No difference in clinical (94% vs 83%) or microbiological (76% vs 80%) cure rates
Grant et al., 2002 (70)	Prospective, open label, controlled	98/mixed infections	GPB + GNB	TZP 8–12 g/day CI vs TZP 3–4 g q6–8h II	No difference in clinical (94% vs 82%) or microbiological (89% vs 73%) cure rates
Rafati et al., 2006 (61)	RCT	40/septic, critically ill	GNB	PIP 8 g/day CI vs PIP 3 g q6h II	Significant reductions in severity of illness (APACHE II)
Lau et al., 2006 (62)	Randomized, multicenter, open label	262/complicated intra-abdominal infections	GBP + GNB	TZP 12 g/day CI vs TZP 3 g q6h II	No difference in clinical (86.4% vs 88.4%) or microbiological (83.9% vs 87.9%) cure rates
Lorente et al., 2006 (78)	Retrospective, single center	89/VAP	GNB	MEM 4 g/day CI vs MEM 1 g q6h II	Significantly greater clinical cure rate (90.5% vs 59.6%)
Lorente et al., 2007 (79)	Retrospective, single center	121/VAP	GNB	CAZ 4 g/day CI vs CAZ 2 g q12h II	Significantly greater clinical cure rate (89.3% vs 52.3%)
Roberts et al., 2007 (58)	RCT	57/septic, critically ill	GPB + GNB	CRO 2 g/day CI vs CRO 2 g q24h II	Significantly greater clinical and bacteriological cure rates only in patients receiving 4 or more days of treatment
Sakka et al., 2007 (60)	RCT	20/nosocomial pneumonia	GPB + GNB	IMI 2 g/day CI vs IMI 1 g q8h II	No difference in mortality
van Zanten et al., 2007 (59)	RCT	93/COPD exacerbation	GPB + GNB	CTX 2 g/day CI vs CTX 1 g q8h II	No difference in clinical cure rate (93% vs 93%)
Lorente et al., 2009 (80)	Retrospective, single center	83/VAP	GNB	TZP 16 g/day CI vs 4 g q6h II	Significantly greater clinical cure rate only when MIC of the pathogen 8–16 mg/liter
Chytra et al., 2012 (81)	RCT	240/septic, critically ill	GPB + GNB	MEM 4 g/day CI vs 2 g q8h II	No difference in clinical cure rate (83% vs 75%); significantly greater microbiological rate cure (90.6% vs 78.4%)
Dulhunty et al., 2013 (86)	RCT	60/septic, critically ill	GPB + GNB	TZP/MEM/TIM CI vs same drugs II	Significantly greater clinical cure rate (70% vs 43%)
Laterre et al., 2015 (82)	RCT	32/septic, critically ill	GNB	TML 6 g/day CI vs 2 g q8h II	No difference in clinical cure rate (93% vs 79%)
Dulhunty et al., 2015 (87)	RCT	432/septic, critically ill	GPB + GNB	TZP/MEM/TIM CI vs same drugs II	

[a] Abbreviations: CAZ, ceftazidime; FEP, cefepime; CI, continuous infusion; COPD, chronic obstructive pulmonary disease; CRO, ceftriaxone; CTX, cefotaxime; II, intermittent infusion; PIP, piperacillin; TIM, ticarcillin-clavulanate; TML, temocillin; TZP, piperacillin-tazobactam; MEM, meropenem; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria; VAP, ventilator-associated pneumonia; IMI, imipenem-cilastatin; q6h, every 6 h; RCT, randomized controlled trial; APACHE II, acute physiology and chronic health evaluation II.

continuous-infusion beta-lactam dosing regimens to traditional regimens.

Meta-analysis and systematic critical reviews are of special interest regarding the comparison of beta-lactam infusion dosing strategies in the face of underpowered heterogeneous studies. Although quite a few of these have been conducted over time, they differ markedly in their inclusion/exclusion criteria, thus not necessarily allowing elucidation of the true effectiveness of nontraditional beta-lactam dosing regimens (4, 18, 88–102). Recent meta-analyses that focused on beta-lactams (Table 3) have mostly concluded that existing data were favorable for the use of specific or all beta-lactam agents by prolonged or continuous infusion in terms of clinical outcomes. Although 2 of these studies did not observe a clinical advantage for using continuous or extended schedules (93, 97), the investigators acknowledged the many limitations of the studies included and the need for the larger, multicenter randomized control trials.

To summarize, there is a solid scientific basis and unanimous agreement at the level of preclinical studies that nontraditional dosing of beta-lactams is advantageous over intermittent dosing. The accumulating clinical evidence is not yet conclusive but suggests that there will be certain patient populations that may benefit more than others. The patients who appear to benefit the most from these dosing regimens seem to be sicker, with more severe infections, and infected with bacteria that have higher antibiotic MICs. Notably, many of the studies that were unable to demonstrate superiority of nontraditional dosing have been limited by inclusion of heterogeneous patient populations, infection with low-MIC pathogens, small numbers, and numerous confounding factors, including use of other antibacterials. That being said, the concepts of nontraditional dosing advantages have been adopted successfully by some health care organizations; furthermore, optimized dosing based on PD concepts is recommended in the antimicrobial stewardship guidelines published by the Infectious Diseases Society of America and Society of Healthcare Epidemiology of America (103). A recent random-sample survey among 1,000 hospital pharmacists in the United States found that 11.2% and 5.8% of hospitals reported using continuous and extended infusions, respectively (104). Another survey of 105 Belgian hospitals reported that extended and prolonged modes of administration were used by 10 to 44% of non-intensive care units and by 35 to 81% of the intensive care unit wards included (105).

A large-scale, adequately designed and powered study for getting definite answers and defining the indications is still needed

TABLE 2 Summary of main clinical studies comparing prolonged infusion to intermittent infusion of beta-lactams[a]

Reference	Study design	No. of patients/illness	Microbiological findings	Dosing regimen	Major endpoint findings
Lodise et al., 2007 (69)	Retrospective, single center	194/variable *P. aeruginosa* infections	*P. aeruginosa*	TZP 3.375 g q8h 4-h inf vs TZP 3.375 g q8h or q6h 30-min inf	Significantly lower mortality (12.2% vs 31.6%) in patients with APACHE II score of ≥17
Itabashi, 2007 (84)	Prospective, single center	42/severe pneumonia	GPB + GNB	MEM 500 mg q12h 4-h inf vs MEM 500 mg q12h 1-h inf	Significantly lower mortality (5.6% vs 37.5%)
Chastre et al., 2008 (53)	Prospective, multicenter, randomized	531/VAP	GPB + GNB	DOR 500 mg q8h 4-h inf vs IMI 500 mg q6h 30-min inf or IMI 1 g q8h 1-h inf	Comparable clinical (68.3% vs 64.8%) and microbiological (73.3% vs 67.3%) cure rates; no difference in mortality (10.8% vs 9.5%)
Patel et al., 2009 (71)	Retrospective, multicenter	129/mixed infections (mainly UTI and respiratory tract infection)	GNB	TZP 3.375 g q8h 4-h inf vs TZP 3.375–4.5 g q6h or q8h 30-min inf	No difference in mortality (5.7% vs 8.5%)
Wang 2009 (85)	Retrospective, single center	30/HAP (ICU only)	*Acinetobacter baumannii*	MEM 500 mg q6h 3-h inf vs MEM 1 g q8h 1-h inf	No difference in clinical response
Nicasio et al., 2010 (56)	Prospective, single center	168/VAP	GPB + GNB	Empirical VAP pathway with PI β-lactam vs empirical VAP therapy with II β-lactam	Significantly lower infection-related mortality (8.5% vs 21.6%)
Dow et al., 2011 (83)	Retrospective, single center	121/ICU	GNB	TZP 3.375 g q8h or MEM 500 mg q6h 3- or 4-h inf vs TZP 3.375 g q6h or MEM 500 mg q6h 30-min inf	No difference in mortality (12.4% vs 20.7%)
Esterly et al., 2012 (72)	Retrospective, single center	71/bacteremia	*Acinetobacter baumannii*, *P. aeruginosa*, *Enterobacteriaceae*	IMI or MEM 3-h inf vs IMI or MEM 30-min inf	No difference in mortality (28.6% vs 24.1%)
Kollef et al., 2012 (75)	Prospective, multicenter, randomized	274/VAP	GNB	DOR 1 g q8h 4-h inf for 7 days vs IMI 1 g q8h 1-h inf for 10 days	Clinical cure (45.6% vs 56.8%) numerically lower and 28-day mortality numerically higher (21.5% vs 14.8%) in DOR treatment arm
Lee et al., 2012 (73)	Retrospective, multicenter	148/ICU	GNB	TZP 3.375 g q8h 4-h inf vs TZP 2.25–4.5 g q6–8h 30-min inf	Significantly lower 30-day mortality (19% vs 38%)
Arnold et al., 2013 (76)	Single center, before-after trial	503/ICU	GNB	FEP 2 g q8h or MEM 1 g q8h or TZP 4.5 g q6h as 3-h inf vs same regimen as 30-min inf	Comparable clinical (51% vs 56.6%) and microbiological (49.5% vs 55.2%) cure rates; no difference in 30-day mortality (25.7% vs 23.6%)
Bauer et al., 2013 (77)	Retrospective, single center	304/*P. aeruginosa* bacteremia and/or pneumonia	*P. aeruginosa*	FEP 2 g q8h as 4-h inf vs FEP 2 g q8h as 30-min inf	Significantly lower mortality (20% vs 3%)

[a] Abbreviations: ICU, intensive care unit;; FEP, cefepime; TZP, piperacillin-tazobactam; MEM, meropenem; inf, infusion; q8h, every 8 h; VAP, ventilator-associated pneumonia; DOR, doripenem; IMI, imipenem-cilastatin; q6h, every 6 h; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria; II, intermittent infusion; PI, prolonged infusion; APACHE II, acute physiology and chronic health evaluation II; UTI, urinary tract infection; HAP, hospital-acquired pneumonia.

TABLE 3 Summary of recent meta-analyses that focused on clinical studies of continuous infusion and prolonged infusion of beta-lactams[a]

Reference	Study design(s)/no. of studies	Beta-lactam class(es)	No. of patients analyzed for each outcome (mortality/clinical cure)	Mortality (RR/95% CI)	Clinical cure (RR/95% CI)
Tamma et al., 2011(93)	RCT/14	Pcn, Ceph, Car	982/1,380	0.92/0.61–1.37	1.00/0.94–1.06
Falagas et al., 2013 (4)	RCT/3; retrospective/8; prospective/3	Pcn, Car	1,116/557	0.59/0.41–0.83	1.13/0.99–1.28
Korbila et al., 2013 (97)	RCT/10; retrospective/1	Ceph	914/496	0.96/0.8–1.15	1.14/0.94–1.37
Teo et al., 2014 (99)	RCT/18; prospective/3; retrospective/8	Pcn, Ceph, Car	1,620/1,546	0.66/0.53–0.83	1.12/1.03–1.21
Yang et al., 2015 (100)	RCT/5; prospective/2; retrospective/7	Pcn	1,591/718	0.67/0.5–0.89	1.88/1.29–2.73
Roberts et al. 2016 (102)	RCT/3	Pcn, Car	632/632	0.74/0.56–1	1.2/1.03–1.4

[a] Abbreviations: RCT, randomized controlled trial; Pcn, penicillin; Ceph, cephalosporin; Car, carbapenem; RR, relative risk; CI, confidence interval.

(87). Such a study should include a dosing regimen tailored for each recruiting site, based on the specific local MIC distribution, and pharmacodynamic modeling. A pertinent methodological illustration is the study conducted by Nicasio and colleagues (56) implementing a clinical pathway based on pharmacodynamic considerations and local epidemiology for empirical antibiotic selection for ventilator-associated pneumonia. In this prospective, albeit observational, nonrandomized study, a PD approach was used to determine which antibiotic regimen would be the most appropriate based on local *P. aeruginosa* MICs. An empirical treatment with either 3-h infusions of cefepime at 2 g q8h or meropenem at 2 g q8h plus vancomycin and tobramycin was selected. The 94 patients receiving this treatment had a 69% reduction in infection-related mortality (8.5% versus 21.6%; $P = 0.029$) and a significantly shorter length of stay compared with an historical cohort (56). Since a project of that magnitude is not expected to be finalized in the near future, clinicians should make contemporary use of the evidence gathered so far for optimizing the treatment of difficult-to-handle patients.

ROLE OF THE CLINICAL LABORATORY

The clinical laboratory has always held a critical responsibility in the management of infection. This role continues to expand, now with the emergence of antimicrobial stewardship programs at many hospitals and a call for their presence in all acute-care facilities by 2020. Clinical microbiologists and other members of the laboratory are often members of the stewardship team, a position well justified based on the importance of diagnostics and various reporting strategies in identifying and managing resistant infections (103). With respect to nontraditional strategies to administer beta-lactams, we believe that the clinical laboratory can provide additional services to assist in optimizing beta-lactam dosing. Additionally, it is worthwhile to understand some of the implications that such dosing may have for current laboratory tests.

Blood Culture Neutralization and Time to Detection

It is notable that clinical laboratories are moving toward more molecular tests to quickly identify specific resistant bacteria (106). However, the standard identification techniques for isolating and growing bacteria before further identification and susceptibility testing will remain for some time into the future. Blood cultures, for example, are initially tested in a number of automated systems, such as BD Bactec (Becton, Dickinson and Company) or BacT/Alert (bioMérieux Inc.). These systems contain various binding resins and proprietary materials to prevent antibiotic carryover and inhibition of bacteria. However, the concentration of antibiotic and the duration that concentrations remain elevated may influence the time to positivity or overall positivity of some systems (107–111). A recent study that compared head to head the blood culture media of BacT/Alert Fan and Bactec Plus found the former to be superior in the ability to neutralize peak and middle simulated concentrations of piperacillin. Moreover, in three of nine (33%) discordant scenarios in which bacteria were recovered only from Bactec bottles, lingering piperacillin concentrations greater than the MIC were observed in the BacT/Alert Fan bottles, presumably inhibiting pathogen growth (109). In another study, time to detection for resin-containing blood culture bottles of BacT/Alert FAN with or without defined concentrations of various antimicrobials was investigated. Using a predefined, clinically relevant 3-h delay in the time to positivity, it was found that piperacillin-tazobactam was incompletely neutralized, and some strains did not demonstrate growth in bottles containing the beta-lactam antibiotics, i.e., amoxicillin-clavulanate, cefepime, cefotaxime, and meropenem (110). Importantly, the use of prolonged or continuous beta-lactam administration, combined with more aggressive doses, will result in longer intervals of higher antibiotic concentrations than with traditional intermittent dosing (13) (Fig. 1). Therefore, there is a much higher likelihood of collecting a blood culture specimen that contains antibiotic concentrations skewed to the high levels at any time point, which in turn may result in a delay in time to detection for the blood culture bottle or even potentially a false-negative result. Although it is difficult to predict the implications of nontraditional dosing because no studies have been conducted at this time, it may be worthwhile for labs to take note of any delays in positivity or declines in bacteremia rates after initiation of prolonged- or continuous-infusion protocols. Additional molecular testing may serve to supplement early results, but again, to our knowledge, the effects of active antibiotics remaining in the bottle on molecular testing have also not been studied. This should be an area of further focus for clinical laboratory research.

The Beta-Lactam MIC: Phenotypic Profiling

Knowing the MIC is crucial for the use of a more individualized, patient-centered PK/PD approach. The MIC, as much as it is a cornerstone as a measure of antimicrobial potency, is far from perfect. It has an inherent weakness of being derived from an *in vitro* process that incorporates a fixed drug concentration combined with a standardized inoculum in broth medium that is not representative of real life conditions (for instance, the absence of binding proteins). Nonetheless, some of the major downsides of the MIC, such as the inability to distinguish between antibacterials with time-dependent bactericidal activity versus concentration-dependent bactericidal activity, can be overcome by incorporating PD insights into the clinical decision process (112).

The provision of susceptibility testing results in breakpoints as

the single reporting form by high-throughput automatic systems is the rule with most contemporary clinical laboratories (113). Therefore, MICs across a broad range are often not available. More recently, PD considerations have been taken into account in the process of susceptibility breakpoint determination, as exemplified by the breakpoint determination for parenteral penicillin and some oral beta-lactams against *Streptococcus pneumoniae*, the lowering of piperacillin-tazobactam susceptibility for *P. aeruginosa* from 64 μg/ml to 16 μg/ml, and the new carbapenem breakpoints of ≤2 μg/ml against *P. aeruginosa* (104, 112, 114–116). Although this is a highly desirable process which provides breakpoints that are very reasonable for defining the general utility of an antibiotic against a given organism, having a specific MIC is irreplaceable when developing an individualized regimen. To begin with, there are a number of different approaches for establishing breakpoints, and there are some disagreements between the different agencies that determine them (117). Furthermore, having a sensitivity or resistance breakpoint does not give the full information to the clinician. For instance, a report of "R" in a case of meropenem for *P. aeruginosa* would imply resistance (MIC, ≥8 μg/ml) but fails to disclose whether the MIC is indeed 8 μg/ml (and the infection potentially treatable with a higher PD optimized dosing regimen) or 64 μg/ml, for which successful treatment would be unobtainable with even the most aggressive clinically utilized regimens. Likewise, a report of "S," in the same scenario, does not reveal whether the MIC is 2 μg/ml (at the border of nonsusceptible) or 0.25 μg/ml, against which most regimens should provide PD attainment. The optimization of both empirical and specific antibiotic therapy may be compromised when MICs are not available. In contrast, the appreciation for misinterpretation of the MIC by an unknowledgeable prescriber must be balanced with the clinical laboratory's reporting strategy.

Mohr and colleagues (118) practiced the use of local MICs in a study that involved intensive care unit patients with nosocomial infections due to various Gram-negative bacteria. Following the administration of empirical antibiotic therapy selected by the attending physician, it was exchanged by a targeted treatment regimen based on PD considerations and the specific MIC of the culprit bacteria of each of the 19 subjects included in the study. Improved clinical and microbiological responses were observed in this group of moderately to moderately severely ill patients. Although the interpretation of the findings is limited due to the lack of a control group, the study highlights that the empirical therapy administered before the intervention was suboptimal in many scenarios and that optimal therapy can be designed with the methods described.

A second look at the study by Nicasio and colleagues (56) mentioned above can exemplify these points in the case of optimizing beta-lactam therapy by nontraditional infusions. The incentive of the researchers for developing and successfully implementing a PD-based ventilator-associated pneumonia clinical pathway in our institution's ICUs was a challenging situation: the etiology of an unusually high proportion of all pneumonia episodes was multidrug-resistant bacteria. Using Monte Carlo simulation and broth dilution-based MICs of the causative bacteria, concentration-time curves were derived for standard dosing regimens of several antibiotics, mostly beta-lactams (cefepime, ceftazidime, meropenem, and piperacillin-tazobactam), as well as nontraditional, higher antibiotic doses combined with prolonged- or continuous-infusion regimens. After obtaining 5,000 steady-state profiles, a calculation of the specific PTA for each beta-lactam was conducted. Importantly to the point in issue, the PTA was weighted by the MIC distribution of *P. aeruginosa* in each of the intensive care units investigated, for targeting the most resistant bacteria in developing an empirical regimen. This approach resulted in the use of nontraditional regimens, including extended-infusion cefepime and meropenem and the continuous infusion of piperacillin-tazobactam empirically. Because the MIC distribution was different in each of the ICUs, a different empirical regimen was employed in each. In the surgical and neurotrauma intensive care units, cefepime at 2 g q8h as a prolonged infusion was selected as the first-line regimen, whereas a prolonged infusion of meropenem at 2 g q8h was required in the medical intensive care unit. Thus, an optimal highest probability of treatment success against the local pathogens could be attained. Moreover, the use of specific MICs instead of breakpoints, combined with the PK/PD considerations as discussed above, resulted in successful combination treatments, containing nontraditional beta-lactam regimens, of several patients that had a documented infection with a resistant (according to CLSI breakpoints at the time) *P. aeruginosa* strain. That subgroup of patients would need a much more toxic and less reliable treatment if the strain was declared resistant by use of the standard breakpoints (e.g., the successful treatment of a 78-year-old patient using cefepime at 2 g q8h as a prolonged infusion against a *P. aeruginosa* strain with a cefepime MIC of 16 μg/ml).

Although using the gold-standard broth microdilution technique, for full-range MIC elucidation would definitely be optimal, it is labor-intensive and unlikely to be implemented in most clinical laboratories. Automated systems can produce, at times with an accessory panel, an abbreviated range MIC range for each antibiotic (a dilution or two above or typically below the breakpoints) (119–122), but as discussed above, this is not sufficient for every needed scenario. An appropriate tool could be the Etest (123), which provides a full MIC range and is more feasible in the clinical setting. We would like to suggest the approach of initially conduct testing with the automated system in regular use and then using supplemental Etest MICs for cases in need that test out on the high range of the automated MIC or where a multidrug-resistant phenotypic profile is observed.

Beyond the MIC: Genotypic Profiling

A promising novel field for the clinical laboratory, which is in direct discordance with application of traditional MIC breakpoints, is the application of genotypic profiling and dissociation between *in vitro* and *in vivo* resistance. Recently, Ghazi and colleagues (124) observed that despite a high MIC indicative of meropenem resistance due to Verona integrin-encoded metallo-beta-lactamase (VIM) in *Enterobacteriaceae*, treatment with this antibiotic resulted in unexpected bactericidal activity when used in a humanized high-dose regimen in a murine infection model. Additional examples with gram-negative bacteria harboring the New Delhi metallo-beta-lactamase (NDM) have also been published and supported by a review of the clinical literature surrounding successful treatment with carbapenems for NDM infections (125).

In contrast to the above examples, a genotypic test identifying a *Klebsiella*-producing carbapenemase (KPC) could also lead to avoidance of carbapenem therapies, not only because of phenotypic resistance but because the PD target may be different from

that of non-KPC producing isolates, unattainable, or both. For example, a prolonged infusion of high-dose meropenem (2 g q8h, with each dose infused over 3 h) achieves a high likelihood of obtaining a 40% $fT>$MIC against bacteria with MICs of ≤16 μg/ml. Theoretically, therefore, this meropenem regimen should kill KPC-producing bacteria with MICs of 16 μg/ml or less. However, this hypothesis was not proven accurate in an *in vitro* experiment simulating human exposures to this regimen. While meropenem did achieve a ≥3-log CFU reduction over the initial 6 h against the KPC isolates, regrowth followed in 9 of the 11 isolates. In comparison, significantly greater CFU reductions were observed and maintained against the 6 *P. aeruginosa* isolates matched by MIC (126). A similar result was observed in another *in vitro* pharmacodynamic study, in which monotherapy with prolonged-infusion meropenem failed to preserve bactericidal reductions in CFU over 48 h when tested against 5 KPC-producing isolates, including 4 with meropenem MICs of 8 to 16 μg/ml (127). The combination regimen of meropenem plus tigecycline achieved significantly delayed regrowth comparatively. These data collectively suggest that the PD exposure required for KPC-producing bacteria may be different from that for non-KPC organisms and that monotherapy with a carbapenem for KPC-producing bacteria, at least at doses of ≤6 g/day, should be avoided.

Rapid, automated tools for identification of resistance genes of Gram-negative bacteria are already FDA approved and available. These include the FilmArray blood culture identification panel (BioFire Diagnostics LLC, Salt Lake City, UT) (128), the Verigene Gram-negative blood culture test (Nanosphere Inc., Northbrook, IL) (129), and more recently, the Xpert Carba-R test (Cepheid Inc., Sunnyvale, CA) (130). While the first assay can detect solely the presence of bla_{KPC}, the two other systems are able to detect additional drug resistance genes, among them the bla_{NDM} gene and the bla_{VIM} gene mentioned above (128–130). Although further research is needed, these results suggest that laboratory testing and finding of certain resistance genotypes would imply that the phenotypic resistance is different; thus, antibiotics that are considered "unusable" may in fact be clinically useful, especially when administered as nontraditional doses.

It is clear from the above discussion that for optimally designing the treatment regimen in complicated cases, availability of the local MIC, and at times the genotypic profile, would be helpful.

Therapeutic Drug Monitoring

After considering MIC, the other half of the PK/PD equation is antibiotic concentration, as dictated by the individual pharmacokinetics of the patient. Empirical dosing schedules almost always originate from studies in healthy volunteers, and these regimens are not always representative of different real-world infected patient populations. In critically ill patients, there are marked pathophysiological changes that affect pharmacokinetics. An extensive review of this subject was recently published by Roberts and colleagues (11), but several pertinent examples follow. Systemic inflammatory response syndrome results in third-space sequestration, with resulting hypotension, leading in many cases to administration of large infusion volumes for resuscitation, all of which culminate in increased interstitial volume. For hydrophilic antibiotics such as the beta-lactams, these increases may result in lower intravascular drug concentrations (i.e., larger volumes of distribution) than in patients who are not critically ill and therefore may lead to underdosing (131). Renal and hepatic dysfunctions are usually accounted for when dosing antibiotics, with reduction of the doses, but an opposite phenomenon may be observed in some severely ill patients who develop augmented renal clearance and eliminate some antibiotics more quickly (132). These patients, in theory, may require doses greater than the standard regimen used with normal kidney function. Utilizing PD considerations, such as prolonged and continuous infusion, and the local and individual pathogen MIC is a worthwhile means toward that ultimate goal of treatment optimization. Nevertheless, for overcoming the aforementioned obstacles, the incorporation of drug concentration results through therapeutic drug monitoring (TDM) makes it possible to confirm that exposure thresholds are achieved and adjust dosing regimens as required based on individual pharmacokinetics.

Clinical laboratories and clinicians are accustomed to relate TDM to aminoglycosides and vancomycin. TDM is used for both optimal dosing and toxicity monitoring of these drugs but is traditionally perceived mainly as related to the latter. Because beta-lactams generally have an excellent safety profile, beside some concerns regarding convulsive promotion at very high dosages (133), the optimization of exposure would be the main incentive for using TDM. In the DALI study, it was demonstrated that beta-lactam concentrations in many intensive care unit patients (up to 50%) fell below PD targets (134). Although this was a point-prevalence study without interventional optimal beta-lactam dosing, its conclusions can undoubtedly be extended to support the need for monitoring antibiotic levels even when individual PK/PD considerations are employed. Patel and colleagues found in a prospective study including 50 burn patients that the trough concentrations of beta-lactams were less than the target MIC in 60% of the patients, thus suggesting the need for dose adjustment (135). Another prospective study by Aubert and colleagues reported that serum ceftazidime concentrations among 92 ICU patients were lower than target MICs in 37% of patients and excessive in 27% of them (136).

While TDM for beta-lactams is appealing, it has not come into significant practical use. A recent survey approached 11 institutions worldwide that were known to practice these methods and found high diversity regarding the specific beta-lactam measured, types of patients tested, and drug assay method (137); moreover, the total number of hospitals routinely performing beta-lactam TDM worldwide was estimated to be as few as 30 centers (138). The reason for these figures is multifactorial. First, there is yet no solid proof for a clinical advantage of using beta-lactam serum levels for guiding treatment. Second, the analysis of the serum concentrations of these drugs is carried out by chromatograph-based methods (139, 140), with downsides of relatively long turnaround time (6 to 24 h) and expensive equipment requiring skilled operators (138–140). To illustrate, the cost of measuring one beta-lactam serum concentration was recently estimated at around 30 U.S. dollars per assay (approximately 20 euros) in a central laboratory (138). Despite the apparent obstacles that are shared with the incorporation of most new medical technologies and procedures, clinical laboratories striving to optimize the ultimate goal of patient treatment should not be discouraged. Rather, TDM of beta-lactams is something to consider when bringing on the nontraditional dosing regimens in order to maximize efficacy. A catalyst for using beta-lactam TDM is the apparent advancement in computer software that enables clinicians to use drug concentration data to the greatest benefits possible, without exhaustive pre-

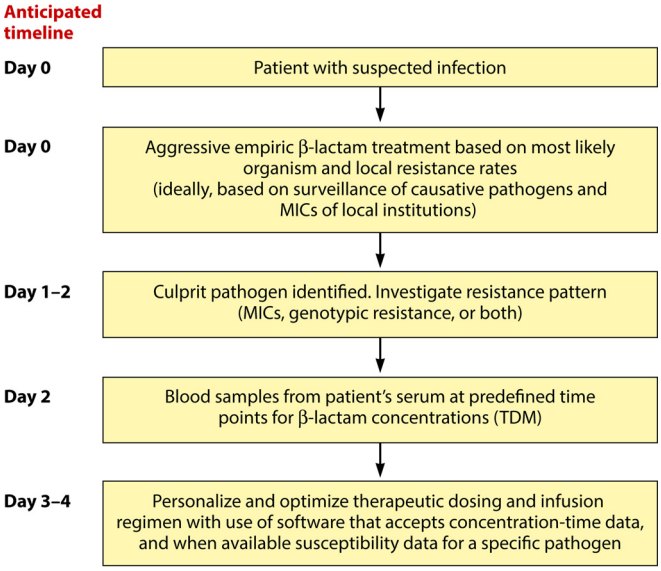


FIG 2 Hypothetical flowchart for optimizing beta-lactam antibiotics in critically ill patients.

vious training. Using Bayesian or nonlinear regression, one can use the patient's own data for adjusting beta-lactam dosage, and some programs allow even the incorporation of population pharmacokinetic data, including local data, to optimize performance (11, 141). Notably, interpretation of levels produced by the laboratory should be by collaboration with clinicians knowledgeable in PD concepts and, ideally, with consideration of the MIC.

We demonstrate the use of all the above-described tools using both a formal flowchart (Fig. 2) and a vivid example of a real case that was treated at our institute. The patient was an adult male with cystic fibrosis admitted with an acute pulmonary exacerbation, presumably due to a multidrug-resistant *Burkholderia cepacia* strain according to latest respiratory cultures, including a meropenem MIC of 16 μg/ml and no effective synergistic or additive antibiotic combination. Given the clinical scenario, an optimized dosing regimen was designed based on the patient's individual pharmacokinetic profile (i.e., TDM), resulting in the eventual administration of meropenem at 2 g q8h as a prolonged 3-h infusion. The patient had a prompt response to treatment, with a clinical improvement beginning on the second day of his hospitalization. The selected meropenem dosing regimen resulted in attainment of a 40% $T>$MIC at the MIC of 16 μg/ml. Sputum cultures confirmed infection with *B. cepacia*, with a meropenem MIC of 8 μg/ml (defined as intermediate at the time) and no synergism or additive antibiotic combination efficacy. The $T>$MIC achieved with the prolonged-infusion meropenem regimen was recalculated to be 52%, further supporting the selected regimen (142).

CONCLUSIONS

Prolonged- and continuous-infusion dosing regimens for beta-lactams have a strong scientific basis that is supported by *in vitro*, *in vivo* animal, and human clinical trials. For achieving optimal exposure with these dosing strategies, coordination between clinicians, the pharmacy, and, importantly, the clinical laboratory is needed. The clinical laboratory can play a pertinent role by analyzing and providing data needed throughout all stages, including microbiological (exact MICs and resistance) and pharmacological (drug concentrations) data. It is imperative that the ultimate interpretation and optimal use of the data reported by the clinical laboratory at the patient bedside relies on a coordinated, seamless process which involves every member of the antimicrobial stewardship team.

Although the implementation of prolonged- and continuous-infusion beta-lactam dosing regimens may be challenging in the hospital setting, it rewards the population that is most at need, i.e., critically ill patients with the greatest risk of multidrug-resistant organisms and fluctuations in PK. The use of these dosing regimens is congruent with focused efforts for a more personalized medicine. Future research in this field should concentrate on further defining benefits in specific clinical populations. As knowledge of the pathogen MIC and individual pharmacokinetics is paramount to optimization of these dosing regimens, the clinical laboratory will continue to play a vital role in successful utilization.

REFERENCES

1. **IDSA.** 2011. IDSA: facts about antibiotic resistance. http://www.idsociety.org/AR_Facts/#. Accessed 30 December 2015.
2. **WHO.** 2014. Antimicrobial resistance: global report on surveillance 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1. Accessed 30 December 2015.
3. **Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J.** 2009. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis **48:**1–12. http://dx.doi.org/10.1086/595011.
4. **Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ.** 2013. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin Infect Dis **56:**272–282. http://dx.doi.org/10.1093/cid/cis857.
5. **Felton TW, Hope WW, Lomaestro BM, Butterfield JM, Kwa AL, Drusano GL, Lodise TP.** 2012. Population pharmacokinetics of extended-infusion piperacillin-tazobactam in hospitalized patients with nosocomial infections. Antimicrob Agents Chemother **56:**4087–4094. http://dx.doi.org/10.1128/AAC.00521-12.
6. **Georges B, Conil JM, Ruiz S, Seguin T, Cougot P, Fourcade O, Houin G, Saivin S.** 2012. Ceftazidime dosage regimen in intensive care unit patients: from a population pharmacokinetic approach to clinical practice via Monte Carlo simulations. Br J Clin Pharmacol **73:**588–596. http://dx.doi.org/10.1111/j.1365-2125.2011.04117.x.
7. **MacGowan A.** 2011. Revisiting beta-lactams—PK/PD improves dosing of old antibiotics. Curr Opin Pharmacol **11:**470–476. http://dx.doi.org/10.1016/j.coph.2011.07.006.
8. **Lee LS, Kinzig-Schippers M, Nafziger AN, Ma L, Sörgel F, Jones RN, Drusano GL, Bertino JS, Jr.** 2010. Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. Diagn Microbiol Infect Dis **68:**251–258. http://dx.doi.org/10.1016/j.diagmicrobio.2010.06.012.
9. **Landersdorfer CB, Kirkpatrick CM, Kinzig-Schippers M, Bulitta JB, Holzgrabe U, Drusano GL, Sörgel F.** 2007. Population pharmacokinetics at two dose levels and pharmacodynamic profiling of flucloxacillin. Antimicrob Agents Chemother **51:**3290–3297. http://dx.doi.org/10.1128/AAC.01410-06.
10. **Drusano GL.** 2007. Pharmacokinetics and pharmacodynamics of antimicrobials. Clin Infect Dis **45**(Suppl 1)**:**S89–S95. http://dx.doi.org/10.1086/518137.
11. **Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL.** 2014. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis **14:**498–509. http://dx.doi.org/10.1016/S1473-3099(14)70036-2.
12. **Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Pediatric Infectious Diseases Society.** 2012. Policy

statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol **33:**322–327. http://dx.doi.org/10.1086/665010.

13. **Turnidge JD.** 1998. The pharmacodynamics of beta-lactams. Clin Infect Dis **27:**10–22. http://dx.doi.org/10.1086/514622.
14. **Drusano GL.** 2004. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol **2:**289–300. http://dx.doi.org/10.1038/nrmicro862.
15. **Ong CT, Tessier PR, Li C, Nightingale CH, Nicolau DP.** 2007. Comparative in vivo efficacy of meropenem, imipenem, and cefepime against Pseudomonas aeruginosa expressing MexA-MexB-OprM efflux pumps. Diagn Microbiol Infect Dis **57:**153–161. http://dx.doi.org/10.1016/j.diagmicrobio.2006.06.014.
16. **De Waele J, Carlier M, Hoste E, Depuydt P, Decruyenaere J, Wallis SC, Lipman J, Roberts JA.** 2014. Extended versus bolus infusion of meropenem and piperacillin: a pharmacokinetic analysis. Minerva Anestesiol **80:**1302–1309.
17. **Lipš M, Siller M, Strojil J, Urbánek K, Balík M, Suchánková H.** 2014. Pharmacokinetics of imipenem in critically ill patients during empirical treatment of nosocomial pneumonia: a comparison of 0.5-h and 3-h infusions. Int J Antimicrob Agents **44:**358–362. http://dx.doi.org/10.1016/j.ijantimicag.2014.05.011.
18. **Yusuf E, Spapen H, Piérard D.** 2014. Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: a narrative and systematic review. J Crit Care **29:**1089–1095. http://dx.doi.org/10.1016/j.jcrc.2014.07.033.
19. **Roberts JA, Lipman J, Blot S, Rello J.** 2008. Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients? Curr Opin Crit Care **14:**390–396. http://dx.doi.org/10.1097/MCC.0b013e3283021b3a.
20. **Eagle HR, Fleischman R, Levy M.** 1953. "Continuous" vs. "discontinuous" therapy with penicillin: the effect of the interval between injections on therapeutic efficacy. N Engl J Med **8:**481–488.
21. **Eagle HR, Fleischman R, Musselman AD.** 1950. Effect of schedule of administration on the therapeutic efficacy of penicillin: importance of the aggregate time penicillin remains at effectively bactericidal levels. Am J Med **9:**280–299. http://dx.doi.org/10.1016/0002-9343(50)90425-6.
22. **Schmidt LH, Walley A, Larson RD.** 1949. The influence of the dosage regimen on the therapeutic activity of penicillin G. J Pharmacol Exp Ther **96:**258–268.
23. **Craig WA, Ebert SC.** 1992. Continuous infusion of beta-lactam antibiotics. Antimicrob Agents Chemother **36:**2577–2583. http://dx.doi.org/10.1128/AAC.36.12.2577.
24. **Bakker-Woudenberg IA, van den Berg JC, Fontijne P, Michel MF.** 1984. Efficacy of continuous versus intermittent administration of penicillin G in Streptococcus pneumoniae pneumonia in normal and immunodeficient rats. Eur J Clin Microbiol **3:**131–135. http://dx.doi.org/10.1007/BF02014330.
25. **Craig WA, Gudmundsson S.** 1991. Postantibiotic effect, p 403–431. *In* Lorian V (ed), Antibiotics in laboratory medicine, 3rd ed. The Williams &Wilkins Co., Baltimore, MD.
26. **Leggett JE, Fantin B, Ebert S, Totsuka B, Vogelman B, Calame W, Mattie H, Craig WA.** 1989. Comparative antibiotic dose-effect relations at several dosing intervals in murine pneumonitis and thigh-infection models. J Infect Dis **159:**281–292. http://dx.doi.org/10.1093/infdis/159.2.281.
27. **Roosendaal R, Bakker-Woudenberg IA, van den Berg JC, Michel MF.** 1985. Therapeutic efficacy of continuous versus intermittent administration of ceftazidime in an experimental Klebsiella pneumoniae pneumonia in rats. J Infect Dis **152:**373–378. http://dx.doi.org/10.1093/infdis/152.2.373.
28. **Roosendaal R, Bakker-Woudenberg IA, van den Berghe-van Raffe M, Michel MF.** 1986. Continuous versus intermittent administration of ceftazidime in experimental Klebsiella pneumoniae pneumonia in normal and leukopenic rats. Antimicrob Agents Chemother **30:**403–408. http://dx.doi.org/10.1128/AAC.30.3.403.
29. **Mordenti JJ, Quintiliani R, Nightingale CH.** 1985. Combination antibiotic therapy: comparison of constant infusion and intermittent bolus dosing in an experimental animal model. J Antimicrob Chemother **15**(Suppl A)**:**312–313.
30. **White CA, Toothaker RD.** 1985. Influence of ampicillin elimination half-life on in-vitro bactericidal effect. J Antimicrob Chemother **15**(Suppl A)**:**257–260. http://dx.doi.org/10.1093/jac/15.2.257,10.1093/jac/15.suppl_A.257.
31. **Mouton JW, den Hollander JG.** 1994. Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother **38:**931–936. http://dx.doi.org/10.1128/AAC.38.5.931.
32. **Keil S, Wiedemann B.** 1997.Antimicrobial effects of continuous versus intermittent administration of carbapenem antibiotics in an in vitro dynamic model. Antimicrob Agents Chemother **41:**1215–1219.
33. **Bowker KE, Holt HA, Lewis RJ, Reeves DS, MacGowan AP.** 1998. Comparative pharmacodynamics of meropenem using an in-vitro model to simulate once, twice and three times daily dosing in humans. J Antimicrob Chemother **42:**461–467. http://dx.doi.org/10.1093/jac/42.4.461.
34. **Flückiger U, Segessenmann C, Gerber AU.** 1991. Integration of pharmacokinetics and pharmacodynamics of imipenem in a human-adapted mouse model. Antimicrob Agents Chemother **35:**1905–1910. http://dx.doi.org/10.1128/AAC.35.9.1905.
35. **Fuentes F, Martín MM, Izquierdo J, Gomez-Lus ML, Prieto J.** 1995. In vivo and in vitro study of several pharmacodynamic effects of meropenem. Scand J Infect Dis **27:**469–474. http://dx.doi.org/10.3109/00365549509047048.
36. **Elkhaïli H, Peter JD, Pompei D, Levless-Than-Or-Eq Slanteque D, Linger L, Salmon Y, Salmon J, Monteil H.** 1998. Pharmacokinetics in vivo and pharmacodynamics ex vivo/in vitro of meropenem and cefpirome in the Yucatan micropig model: continuous infusion versus intermittent injection. Clin Microbiol Infect **4:**18–26. http://dx.doi.org/10.1111/j.1469-0691.1998.tb00329.x.
37. **MacGowan AP, Bowker KE.** 1998. Continuous infusion of beta-lactam antibiotics. Clin Pharmacokinet **35:**391–402. http://dx.doi.org/10.2165/00003088-199835050-00004.
38. **Leder K, Turnidge JD, Korman TM, Grayson ML.** 1999. The clinical efficacy of continuous-infusion flucloxacillin in serious staphylococcal sepsis. J Antimicrob Chemother **43:**113–118. http://dx.doi.org/10.1093/jac/43.1.113.
39. **Mouton JW, Horrevorts AM, Mulder PG, Prens EP, Michel MF.** 1990. Pharmacokinetics of ceftazidime in serum and suction blister fluid during continuous and intermittent infusions in healthy volunteers. Antimicrob Agents Chemother **34:**2307–2311. http://dx.doi.org/10.1128/AAC.34.12.2307.
40. **Vinks AA, Brimicombe RW, Heijerman HG, Bakker W.** 1997. Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. J Antimicrob Chemother **40:**125–133. http://dx.doi.org/10.1093/jac/40.1.125.
41. **Kuzemko J, Crawford C.** 1989. Continuous infusion of ceftazidime in cystic fibrosis. Lancet **ii:**385.
42. **Daenen S, Erjavec Z, Uges DR, De Vries-Hospers HG, De Jonge P, Halie MR.** 1995. Continuous infusion of ceftazidime in febrile neutropenic patients with acute myeloid leukemia. Eur J Clin Microbiol Infect Dis **14:**188–192. http://dx.doi.org/10.1007/BF02310354.
43. **Benko AS, Cappelletty DM, Kruse JA, Rybak MJ.** 1996. Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected gram-negative infections. Antimicrob Agents Chemother **40:**691–695.
44. **Lipman J, Gomersall CD, Gin T, Joynt GM, Young RJ.** 1999. Continuous infusion ceftazidime in intensive care: a randomized controlled trial. J Antimicrob Chemother **43:**309–311. http://dx.doi.org/10.1093/jac/43.2.309.
45. **Nicolau DP, McNabb J, Lacy MK, Li J, Quintiliani R, Nightingale CH.** 1999. Pharmacokinetics and pharmacodynamics of continuous and intermittent ceftazidime during the treatment of nosocomial pneumonia. Clin Drug Invest **18:**133–139. http://dx.doi.org/10.2165/00044011-199918020-00006.
46. **Nicolau DP, Lacy MK, McNabb J, Quintiliani R, Nightingale CH.** 1998. Pharmacokinetics of continuous and intermittent ceftazidime in intensive care unit patients with nosocomial pneumonia. Infect Dis Clin Pract **8:**45–49.
47. **Thalhammer F, Traunmüller F, El Menyawi I, Frass M, Hollenstein UM, Locker GJ, Stoiser B, Staudinger T, Thalhammer-Scherrer R, Burgmann H.** 1999. Continuous infusion versus intermittent adminis-

tration of meropenem in critically ill patients. J Antimicrob Chemother **43:**523–527. http://dx.doi.org/10.1093/jac/43.4.523.
48. **Bodey GP, Ketchel SJ, Rodriguez V.** 1979. A randomized study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients. Am J Med **67:**608–616. http://dx.doi.org/10.1016/0002-9343(79)90242-0.
49. **Lagast H, Meunier-Carpentier F, Klastersky J.** 1983. Treatment of gram-negative bacillary septicemia with cefoperazone. Eur J Clin Microbiol **2:**554–558. http://dx.doi.org/10.1007/BF02016564.
50. **Dunning J, Roberts J.** 2015. Continuous infusion of beta-lactam antibiotics to treat severe sepsis: a waste of time or worth the hassle? Br J Hosp Med (Lond) **76:**310. http://dx.doi.org/10.12968/hmed.2015.76.5.310.
51. **De Waele JJ, Lipman J, Carlier M, Roberts JA.** 2015. Subtleties in practical application of prolonged infusion of β-lactam antibiotics. Int J Antimicrob Agents **45:**461–463. http://dx.doi.org/10.1016/j.ijantimicag.2015.01.007.
52. **Roberts JA, Kirkpatrick CM, Lipman J.** 2011. Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. J Antimicrob Chemother **66:**227–231. http://dx.doi.org/10.1093/jac/dkq449.
53. **Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I.** 2008. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. Crit Care Med **36:**1089–1096. http://dx.doi.org/10.1097/CCM.0b013e3181691b99.
54. **Shea KM, Cheatham SC, Smith DW, Wack MF, Sowinski KM, Kays MB.** 2009. Comparative pharmacodynamics of intermittent and prolonged infusions of piperacillin/tazobactam using Monte Carlo simulations and steady-state pharmacokinetic data from hospitalized patients. Ann Pharmacother **43:**1747–1754. http://dx.doi.org/10.1345/aph.1M304.
55. **George JM, Towne TG, Rodvold KA.** 2012. Prolonged infusions of β-lactam antibiotics: implication for antimicrobial stewardship. Pharmacotherapy **32:**707–721. http://dx.doi.org/10.1002/j.1875-9114.2012.01157.x.
56. **Nicasio AM, Eagye KJ, Nicolau DP, Shore E, Palter M, Pepe J, Kuti JL.** 2010. Pharmacodynamic-based clinical pathway for empiric antibiotic choice in patients with ventilator-associated pneumonia. J Crit Care **25:**69–77. http://dx.doi.org/10.1016/j.jcrc.2009.02.014.
57. **Buijk SL, Gyssens IC, Mouton JW, Van Vliet A, Verbrugh HA, Bruining HA.** 2002. Pharmacokinetics of ceftazidime in serum and peritoneal exudate during continuous versus intermittent administration to patients with severe intra-abdominal infections. J Antimicrob Chemother **49:**121–128. http://dx.doi.org/10.1093/jac/49.1.121.
58. **Roberts JA, Boots R, Rickard CM, Thomas P, Quinn J, Roberts DM, Richards B, Lipman J.** 2007. Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. J Antimicrob Chemother **59:**285–291.
59. **Van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH.** 2007. Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. Br J Clin Pharmacol **63:**100–109. http://dx.doi.org/10.1111/j.1365-2125.2006.02730.x.
60. **Sakka SG, Glauner AK, Bulitta JB, Kinzig-Schippers M, Pfister W, Drusano GL, Sörgel F.** 2007. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomized, controlled trial. Antimicrob Agents Chemother **51:**3304–3310. http://dx.doi.org/10.1128/AAC.01318-06.
61. **Rafati MR, Rouini MR, Mojtahedzadeh M, Najafi A, Tavakoli H, Gholami K, Fazeli MR.** 2006. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. Int J Antimicrob Agents **28:**122–127. http://dx.doi.org/10.1016/j.ijantimicag.2006.02.020.
62. **Lau WK, Mercer D, Itani KM, Nicolau DP, Kuti JL, Mansfield D, Dana A.** 2006. Randomized, 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 **50:**3556–3561. http://dx.doi.org/10.1128/AAC.50.2.556-564.2006.
63. **Georges B, Conil JM, Cougot P, Decun JF, Archambaud M, Seguin T, Chabanon G, Virenque C, Houin G, Saivin S.** 2005. Cefepime in critically ill patients: continuous infusion vs. an intermittent dosing regimen. Int J Clin Pharmacol Ther **43:**360–369. http://dx.doi.org/10.5414/CPP43360.
64. **Buck C, Bertram N, Ackermann T, Sauerbruch T, Derendorf H, Paar WD.** 2005. Pharmacokinetics of piperacillin-tazobactam: intermittent dosing versus continuous infusion. Int J Antimicrob Agents **25:**62–67. http://dx.doi.org/10.1016/j.ijantimicag.2004.08.012.
65. **Lubasch A, Lück S, Lode H, Mauch H, Lorenz J, Bölcskei P, Welte T, COPD Study Group.** 2003. Optimizing ceftazidime pharmacodynamics in patients with acute exacerbation of severe chronic bronchitis. J Antimicrob Chemother **51:**659–664. http://dx.doi.org/10.1093/jac/dkg111.
66. **Nicolau DP, McNabb J, Lacy MK, Quintiliani R, Nightingale CH.** 2001. Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents **17:**497–504. http://dx.doi.org/10.1016/S0924-8579(01)00329-6.
67. **Hanes SD, Wood GC, Herring V, Croce MA, Fabian TC, Pritchard E, Boucher BA.** 2000. Intermittent and continuous ceftazidime infusion for critically ill trauma patients. Am J Surg **179:**436–440. http://dx.doi.org/10.1016/S0002-9610(00)00388-3.
68. **Angus BJ, Smith MD, Suputtamongkol Y, Mattie H, Walsh AL, Wuthiekanun V, Chaowagul W, White NJ.** 2000. Pharmacokinetic-pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicaemic melioidosis. Br J Clin Pharmacol **50:**184–191. http://dx.doi.org/10.1111/j.1365-2125.2000.00179.x.
69. **Lodise TP, Jr, Lomaestro B, Drusano GL.** 2007. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis **44:**357–363. http://dx.doi.org/10.1086/510590.
70. **Grant EM, Kuti JL, Nicolau DP, Nightingale C, Quintiliani R.** 2002. Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital. Pharmacotherapy **22:**471–483. http://dx.doi.org/10.1592/phco.22.7.471.33665.
71. **Patel GW, Patel N, Lat A, Trombley K, Enbawe S, Manor K, Smith R, Lodise TP, Jr.** 2009. Outcomes of extended infusion piperacillin/tazobactam for documented Gram-negative infections. Diagn Microbiol Infect Dis **64:**236–240. http://dx.doi.org/10.1016/j.diagmicrobio.2009.03.002.
72. **Esterly JS, Wagner J, McLaughlin MM, Postelnick MJ, Qi C, Scheetz MH.** 2012. Evaluation of clinical outcomes in patients with bloodstream infections due to Gram-negative bacteria according to carbapenem MIC stratification. Antimicrob Agents Chemother **56:**4885–4890. http://dx.doi.org/10.1128/AAC.06365-11.
73. **Lee GC, Liou H, Yee R, Quan CF, Neldner K.** 2012. Outcomes of extended-infusion piperacillin-tazobactam: a retrospective analysis of critically ill patients. Clin Ther **34:**2297–2300. http://dx.doi.org/10.1016/j.clinthera.2012.11.005.
74. **Yost RJ, Cappelletty DM, RECEIPT Study Group.** 2011. The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) study: a multicenter study. Pharmacotherapy **31:**767–775. http://dx.doi.org/10.1592/phco.31.8.767.
75. **Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R.** 2012. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. Crit Care **16:**R218. http://dx.doi.org/10.1186/cc11862.
76. **Arnold HM, Hollands JM, Skrupky LP, Smith JR, Juang PH, Hampton NB, McCormick S, Reichley RM, Hoban A, Hoffmann J, Micek ST, Kollef MH.** 2013. Prolonged infusion antibiotics for suspected gram-negative infections in the ICU: a before-after study. Ann Pharmacother **47:**170–180. http://dx.doi.org/10.1345/aph.1R523.
77. **Bauer KA, West JE, O'Brien JM, Goff DA.** 2013. Extended-infusion cefepime reduces mortality in patients with Pseudomonas aeruginosa infections. Antimicrob Agents Chemother **57:**2907–2912. http://dx.doi.org/10.1128/AAC.02365-12.
78. **Lorente L, Lorenzo L, Martin MM, Jimenez A, Mora ML.** 2006. Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to gram-negative bacilli. Ann Pharmacother **40:**219–223. http://dx.doi.org/10.1345/aph.1G467.
79. **Lorente L, Jimenez A, Palmero S, Jimenez JJ, Iribarren JL, Santana M, Martin MM, Mora ML.** 2007. Comparison of clinical cure rates in adults with ventilator-associated pneumonia treated with intravenous ceftazidime administered by continuous or intermittent infusion: a retrospec-

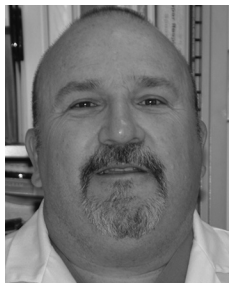
tive, nonrandomized, open-label, historical chart review. Clin Ther **29:** 2433–2439. http://dx.doi.org/10.1016/j.clinthera.2007.11.003.
80. **Lorente L, Jimenez A, Martin MM, Iribarren JL, Jimenez JJ, Mora ML.** 2009. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. Int J Antimicrob Agents **33:**464–468. http://dx.doi.org/10.1016/j.ijantimicag.2008.10.025.
81. **Chytra I, Stepan M, Benes J, Pelnar P, Zidkova A, Bergerova T, Pradl R, Kasal E.** 2012. Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. Crit Care **16:**R113. http://dx.doi.org/10.1186/cc11405.
82. **Laterre PF, Wittebole X, Van de Velde S, Muller AE, Mouton JW, Carryn S, Tulkens PM, Dugernier T.** 2015. Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration. J Antimicrob Chemother **70:**891–898. http://dx.doi.org/10.1093/jac/dku465.
83. **Dow R, Rose W, Fox B.** 2011. Retrospective study of prolonged versus intermittent infusion piperacillin-tazobactam and meropenem in intensive care unit patients at an academic medical center. Infect Dis Clin Pract **19:**413–417. http://dx.doi.org/10.1097/IPC.0b013e31822e9bf5.
84. **Itabashi S.** 2007. Clinical efficacy of prolonged (4 hour) drip infusion of meropenem against severe pneumonia. Jpn J Antibiot **60:**161–170.
85. **Wang D.** 2009. Experience with extended-infusion meropenem in the management of ventilator-associated pneumonia due to multidrug-resistant Acinetobacter baumannii. Int J Antimicrob Agents **33:**290–291. http://dx.doi.org/10.1016/j.ijantimicag.2008.09.012.
86. **Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Lipman J.** 2013. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis **56:**236–244. http://dx.doi.org/10.1093/cid/cis856.
87. **Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Starr T, Paul SK, Lipman J.** 2015. A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis. Am J Respir Crit Care Med **192:** 1298–1305. http://dx.doi.org/10.1164/rccm.201505-0857OC.
88. **Abdul-Aziz MH, Dulhunty JM, Bellomo R, Lipman J, Roberts JA.** 2012. Continuous beta-lactam infusion in critically ill patients: the clinical evidence. Ann Intensive Care **2:**37. http://dx.doi.org/10.1186/2110-5820-2-37.
89. **Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME.** 2005. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis **5:**581–589. http://dx.doi.org/10.1016/S1473-3099(05)70218-8.
90. **Roberts JA, Paratz J, Paratz E, Krueger WA, Lipman J.** 2007. Continuous infusion of beta-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents **30:**111–118.
91. **Roberts JA, Webb S, Paterson D, Ho KM, Lipman J.** 2009. A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med **37:**2071–2078. http://dx.doi.org/10.1097/CCM.0b013e3181a0054d.
92. **Perrott J, Mabasa VH, Ensom MH.** 2010. Comparing outcomes of meropenem administration strategies based on pharmacokinetic and pharmacodynamics principles: a qualitative systematic review. Ann Pharmacother **44:**557–564. http://dx.doi.org/10.1345/aph.1M339.
93. **Tamma PD, Putcha N, Suh YD, Van Arendonk KJ, Rinke ML.** 2011. Does prolonged β-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. BMC Infect Dis **11:**181. http://dx.doi.org/10.1186/1471-2334-11-181.
94. **Mah GT, Mabasa VH, Chow I, Ensom MH.** 2012. Evaluating outcomes associated with alternative dosing strategies for piperacillin/tazobactam: a qualitative systematic review. Ann Pharmacother **46:**265–275. http://dx.doi.org/10.1345/aph.1Q378.
95. **Smuszkiewicz P, Szałek E, Tomczak H, Grzeœkowiak E.** 2013. Continuous infusion of antibiotics in critically ill patients. Curr Clin Pharmacol **8:**13–24. http://dx.doi.org/10.2174/1574884711308010004.
96. **Shiu J, Wang E, Tejani AM, Wasdell M.** 2013. Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. Cochrane Database Syst Rev **3:**CD008481. http://dx.doi.org/10.1002/14651858.CD008481.pub2.
97. **Korbila IP, Tansarli GS, Karageorgopoulos DE, Vardakas KZ, Falagas ME.** 2013. Extended or continuous versus short-term intravenous infusion of cephalosporins: a meta-analysis. Expert Rev Anti Infect Ther **11:**585–595. http://dx.doi.org/10.1586/eri.13.44.
98. **MacVane SH, Kuti JL, Nicolau DP.** 2014. Prolonging β-lactam infusion: a review of the rationale and evidence, and guidance for implementation. Int J Antimicrob Agents **43:**105–113. http://dx.doi.org/10.1016/j.ijantimicag.2013.10.021.
99. **Teo J, Liew Y, Lee W, Kwa AL.** 2014. Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis. Int J Antimicrob Agents **5:**403–411.
100. **Yang H, Zhang C, Zhou Q, Wang Y, Chen L.** 2015. Clinical outcomes with alternative dosing strategies for piperacillin/tazobactam: a systematic review and meta-analysis. PLoS One **10:**e0116769 http://dx.doi.org/10.1371/journal.pone.0116769.
101. **Burgess SV, Mabasa VH, Chow I, Ensom MH.** 2015. Evaluating outcomes of alternative dosing strategies for cefepime: a qualitative systematic review. Ann Pharmacother **49:**311–322. http://dx.doi.org/10.1177/1060028014564179.
102. **Roberts JA, Abdul-Aziz MH, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, Bellomo R, Lipman J.** 14 March 2016. Continuous versus intermittent beta-lactam infusion in severe sepsis: a meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med http://dx.doi.org/10.1164/rccm.201601-0024OC.
103. **Dellit TH, Owens RC, McGowan JE, Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America.** 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis **44:**159–177. http://dx.doi.org/10.1086/510393.
104. **George JM, Colton BJ, Rodvold KA.** 2012. National survey on continuous and extended infusions of antibiotics. Am J Health Syst Pharm **69:**1895–1904. http://dx.doi.org/10.2146/ajhp110562.
105. **Buyle FM, Decruyenaere J, De Waele J, Tulkens PM, Van Audenrode T, Depuydt P, Claeys G, Robays H, Vogelaers D.** 2013. A survey of beta-lactam antibiotics and vancomycin dosing strategies in intensive care units and general wards in Belgian hospitals. Eur J Clin Microbiol Infect Dis **32:**763–768. http://dx.doi.org/10.1007/s10096-012-1803-7.
106. **Sloots TP, Nissen MD, Ginn AN, Iredell JR.** 2015. Rapid identification of pathogens using molecular techniques. Pathology **47:**191–198. http://dx.doi.org/10.1097/PAT.0000000000000241.
107. **Spaargaren J, van Boven CP, Voorn GP.** 1998. Effectiveness of resins in neutralizing antibiotic activities in bactec plus Aerobic/F culture medium. J Clin Microbiol **36:**3731–3713.
108. **Viganò EF, Vasconi E, Agrappi C, Clerici P, Melloni P.** 2004. Use of simulated blood cultures for antibiotic effect on time to detection of the two blood culture systems BacT/ALERT and BACTEC 9240. New Microbiol **27:**235–248.
109. **Zadroga R, Williams DN, Gottschall R, Hanson K, Nordberg V, Deike M, Kuskowski M, Carlson L, Nicolau DP, Sutherland C, Hansen GT.** 2013. Comparison of 2 blood culture media shows significant differences in bacterial recovery for patients on antimicrobial therapy. Clin Infect Dis **56:**790–797. http://dx.doi.org/10.1093/cid/cis1021.
110. **Mitteregger D, Barousch W, Nehr M, Kundi M, Zeitlinger M, Makristathis A, Hirschl AM.** 2013. Neutralization of antimicrobial substances in new BacT/Alert FA and FN Plus blood culture bottles. J Clin Microbiol **51:**1534–1540. http://dx.doi.org/10.1128/JCM.00103-13.
111. **Fiori B, D'Inzeo T, Di Florio V, De Maio F, De Angelis G, Giaquinto A, Campana L, Tanzarella E, Tumbarello M, Antonelli M, Sanguinetti M, Spanu T.** 2014. Performance of two resin-containing blood culture media in detection of bloodstream infections and in direct matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) broth assays for isolate identification: clinical comparison of the BacT/Alert Plus and Bactec Plus systems. J Clin Microbiol **52:**3558–3567. http://dx.doi.org/10.1128/JCM.01171-14.
112. **Owens RC, Jr, Shorr AF.** 2009. Rational dosing of antimicrobial agents: pharmacokinetic and pharmacodynamic strategies. Am J Health Syst Pharm **66:**S23–30. http://dx.doi.org/10.2146/090087d.
113. **Bobenchik AM, Deak E, Hindler JA, Charlton CL, Humphries RM.** 2015. Performance of Vitek 2 for antimicrobial susceptibility testing of

Enterobacteriaceae with Vitek 2 (2009 FDA) and 2014 CLSI breakpoints. J Clin Microbiol **53:**816–823. http://dx.doi.org/10.1128/JCM.02697-14.
114. **Clinical and Laboratory Standards Institute.** 2012. Performance standards for antimicrobial susceptibility testing; twenty-second informational supplement. CLSI document M100–S22. Clinical and Laboratory Standards Institute, Wayne, PA.
115. **Clinical and Laboratory Standards Institute.** 2014. Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement. CLSI document M100–S24. Clinical and Laboratory Standards Institute, Wayne, PA.
116. **Tamma PD, Turnbull AE, Milstone AM, Hsu AJ, Carroll KC, Cosgrove SE.** 2012. Does the piperacillin minimum inhibitory concentration for Pseudomonas aeruginosa influence clinical outcomes of children with pseudomonal bacteremia? Clin Infect Dis **55:**799–806. http://dx.doi.org/10.1093/cid/cis545.
117. **Hombach M, Bloemberg GV, Böttger EC.** 2012. Effects of clinical breakpoint changes in CLSI guidelines 2010/2011 and EUCAST guidelines 2011 on antibiotic susceptibility test reporting of Gram-negative bacilli. J Antimicrob Chemother **67:**622–632. http://dx.doi.org/10.1093/jac/dkr524.
118. **Mohr JF, Wanger A, Rex JH.** 2004. Pharmacokinetic/pharmacodynamic modeling can help guide targeted antimicrobial therapy for nosocomial gram-negative infections in critically ill patients. Diagn Microbiol Infect Dis **48:**125–130. http://dx.doi.org/10.1016/j.diagmicrobio.2003.09.010.
119. **Clinical and Laboratory Standards Institute.** 2009. Performance standards for antimicrobial disk susceptibility tests. Approved standard M2-A10. Clinical and Laboratory Standards Institute, Wayne, PA.
120. **Becton, Dickinson and Company.** 2016. BD Phoenix automated microbiology system. http://www.bd.com/ds/productCenter/IS-Phoenix.asp. Becton, Dickinson and Company, Franklin Lakes, NJ. Accessed 27 December 2015.
121. **bioMérieux.** 2016. Bacterial identification and antibiotic susceptibility testing. VITEK 2. http://www.biomerieux.com/en/bacterial-identification-antibiotic-susceptibility-testing-vitek-2. bioMérieux, Marcy-l'Étoile, France. Accessed 27 December 2015.
122. **Beckman Coulter.** 2016. Microbiology systems. https://www.beckmancoulter.com/wsrportal/wsr/diagnostics/clinical-products/microbiology/microbiology-systems/index.htm. Beckman Coulter, Brea, CA. Accessed 27 December 2015.
123. **Baker CN, Stocker SA, Culver DM, Thornsberry C.** 1991. Comparison of the E-test to agar dilution, broth microdilution, and agar diffusion susceptibility testing techniques by using a special challenge set of bacteria. J Clin Microbiol **29:**533–538.
124. **Ghazi IM, Crandon JL, Lesho EP, McGann P, Nicolau DP.** 2015. Efficacy of humanized high-dose meropenem, cefepime, and levofloxacin against Enterobacteriaceae isolates producing Verona integron-encoded metallo-β-lactamase (VIM) in a murine thigh infection model. Antimicrob Agents Chemother **59:**7145–7147. http://dx.doi.org/10.1128/AAC.00794-15.
125. **Zmarlicka MT, Nailor MD, Nicolau DP.** 2015. Impact of the New Delhi metallo-beta-lactamase on beta-lactam antibiotics. Infect Drug Resist **8:**297–309. http://dx.doi.org/10.2147/IDR.S39186.
126. **Bulik CC, Christensen H, Li P, Sutherland CA, Nicolau DP, Kuti JL.** 2010. 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 **54:**804–810. http://dx.doi.org/10.1128/AAC.01190-09.
127. **Wiskirchen DE, Koomanachai P, Nicasio AM, Nicolau DP, Kuti JL.** 2011. In vitro pharmacodynamics of simulated pulmonary exposures of tigecycline alone and in combination against Klebsiella pneumoniae isolates producing a KPC carbapenemase. Antimicrob Agents Chemother **55:**1420–1427. http://dx.doi.org/10.1128/AAC.01253-10.
128. **BioFire Diagnostics.** 2016. Guidelines for laboratory verification of performance of the FilmArray blood culture identification (BCID) panel. http://www.biofiredx.com/wp-content/uploads/2016/03/TN-FLM1-PRT-0137-04-Guidelines-for-Laboratory-Verification-of-Performance-of-the-FilmArray-Blood-Culture-Identification-Panel.pdf. BioFire Diagnostics, Salt Lake City, UT. Accessed 22 June 2016.
129. **Nanosphere Inc.** 2016. Gram-negative blood culture test. http://www.nanosphere.us/products/gram-negative-blood-culture-test. Nanosphere Inc., Northbrook, IL. Accessed 2 March 2016.
130. **Cepheid.** 2016. Cepheid | Xpert Carba-R. http://www.cepheid.com/en/cepheid-solutions-uk/clinical-ivd-tests/healthcare-associated-infections/xpert-carbar. Cepheid, Sunnyvale, CA. Accessed 2 March 2016.
131. **Gonçalves-Pereira J, Póvoa P.** 2011. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams. Crit Care **15:**R206. http://dx.doi.org/10.1186/cc10441.
132. **Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, Lipman J, Roberts JA.** 2012. Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest **142:**30–39. http://dx.doi.org/10.1378/chest.11-1671.
133. **Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA, Calandra T, Marchetti O.** 2010. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrob Agents Chemother **54:**4360–4367. http://dx.doi.org/10.1128/AAC.01595-08.
134. **Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J, DALI Study.** 2014. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis **58:**1072–1083. http://dx.doi.org/10.1093/cid/ciu027.
135. **Patel BM, Paratz J, See NC, Muller MJ, Rudd M, Paterson D, Briscoe SE, Ungerer J, McWhinney BC, Lipman J, Roberts JA.** 2012. Therapeutic drug monitoring of beta-lactam antibiotics in burns patients—a one-year prospective study. Ther Drug Monit **34:**160–164. http://dx.doi.org/10.1097/FTD.0b013e31824981a6.
136. **Aubert G, Carricajo A, Coudrot M, Guyomarc'h S, Auboyer C, Zeni F.** 2010. Prospective determination of serum ceftazidime concentrations in intensive care units. Ther Drug Monit **32:**517–519. http://dx.doi.org/10.1097/FTD.0b013e3181e60ca6.
137. **Wong G, Brinkman A, Benefield RJ, Carlier M, De Waele JJ, El Helali N, Frey O, Harbarth S, Huttner A, McWhinney B, Misset B, Pea F, Preisenberger J, Roberts MS, Robertson TA, Roehr A, Sime FB, Taccone FS, Ungerer JP, Lipman J, Roberts JA.** 2014. An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother **69:**1416–1423. http://dx.doi.org/10.1093/jac/dkt523.
138. **Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA.** 2015. Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother **70:**3178–3183. http://dx.doi.org/10.1093/jac/dkv201.
139. **Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA.** 2012. Does beta-Lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care **2:**35. http://dx.doi.org/10.1186/2110-5820-2-35.
140. **Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J.** 2010. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents **36:**332–339. http://dx.doi.org/10.1016/j.ijantimicag.2010.06.008.
141. **Fuchs A, Csajka C, Thoma Y, Buclin T, Widmer N.** 2013. Benchmarking therapeutic drug monitoring software: a review of available computer tools. Clin Pharmacokinet **52:**9–22. http://dx.doi.org/10.1007/s40262-012-0020-y.
142. **Kuti JL, Moss KM, Nicolau DP, Knauft RF.** 2004. Empiric treatment of multidrug-resistant Burkholderia cepacia lung exacerbation in a patient with cystic fibrosis: application of pharmacodynamic concepts to meropenem therapy. Pharmacotherapy **24:**1641–1645. http://dx.doi.org/10.1592/phco.24.16.1641.50960.

Continued next page

Mordechai Grupper earned his M.D. from Ben-Gurion University in 1995. He completed a residency in internal medicine at Rambam Medical Center and a fellowship in infectious diseases at the Bnai Zion Medical Center. He served in various positions as a military physician, as a senior infectious diseases clinician for the inpatient infectious diseases service at the Bnai Zion Medical Center, and as a faculty member at the Technion Israel Institute of Technology medical school. During his 8-year career in the infectious diseases field, his main interests have been in optimizing treatment of patients with infectious diseases, hospital epidemiology, and travel medicine. He is currently a research fellow at the Center for Anti-Infective Research and Development, Hartford Hospital, where he is involved in basic and clinical research projects that have direct clinical implications.

Joseph L. Kuti received his Bachelor of Science and Doctor of Pharmacy degrees from Rutgers University College of Pharmacy in Piscataway, NJ. While completing his doctorate, he served as a clinical pharmacist for the medical and surgical intensive care units at Robert Wood Johnson University Hospital in New Brunswick, NJ. He then completed a postdoctoral fellowship in antibiotic management and pharmacoeconomics at Hartford Hospital. For the last 14 years, Dr. Kuti has served as Associate Director of Clinical and Economic Studies at the Center for Anti-Infective Research and Development at Hartford Hospital in Hartford, CT. His primary areas of research include the pharmacokinetics, pharmacodynamics, pharmacoeconomics, and outcomes of antimicrobial therapy in severe infections.



David P. Nicolau is the Director of the Center for Anti-Infective Research and Development at Hartford Hospital in Hartford, CT. After graduating from Northeastern University, he completed a residency in hospital pharmacy at Boston University Medical Center. He then received his Pharm.D. from the Medical University of South Carolina and completed a residency in adult internal medicine at the university's affiliated hospital and a fellowship in infectious diseases at Hartford Hospital. Over 25 years, his research efforts have spanned a range from preclinical drug development studies assessing *in vitro* potency, *in vivo* efficacy, and toxicity profiles of novel compounds to phase I to IV clinical studies. He is also widely recognized for his efforts in the clinical arena, focusing on the development of antimicrobial utilization strategies to improve outcomes and reduce the cost of care. These efforts have been reported in over 600 publications, 425 abstracts, and 1,000 local, national, or international presentations.