

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

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(See the Major Article by Dulhunty et al, on pages 236–44, and the Editorial Commentary by Drusano and Lodise, on pages 245–7.)

We sought to study whether the better pharmacokinetic and pharmacodynamic (PK/PD) properties of carbapenems and piperacillin/tazobactam, when the duration of infusion is longer, were associated with lower mortality. PubMed and Scopus were searched for studies reporting on patients treated with extended (≥ 3 hours) or continuous (24 hours) versus short-term duration (20–60 minutes) infusions of carbapenems or piperacillin/tazobactam. Fourteen studies were included (1229 patients). Mortality was lower among patients receiving extended or continuous infusion of carbapenems or piperacillin/tazobactam compared to those receiving short-term (risk ratio [RR], 0.59; 95% confidence interval [CI], .41–.83). Patients with pneumonia who received extended or continuous infusion had lower mortality than those receiving short-term infusion (RR, 0.50; 95% CI, 0.26–0.96). Data for other specific infections were not available. The available evidence from mainly nonrandomized studies suggests that extended or continuous infusion of carbapenems or piperacillin/tazobactam was associated with lower mortality. Well-designed randomized controlled trials are warranted to confirm these findings before such approaches become widely used.

Keywords. meropenem; imipenem; ertapenem; doripenem.

Carbapenems and piperacillin/tazobactam have been used successfully for the treatment of bacterial infections due to multidrug-resistant pathogens [1–3]. However, many such infections had become difficult to treat and the lack of new promising antibiotics,

especially for the treatment of patients with gram-negative bacterial infections, necessitates the introduction of innovative strategies for the use of antibiotics that are already available. The use of pharmacokinetic-pharmacodynamic (PK/PD) properties of carbapenems and piperacillin/tazobactam could be an effective way to improve clinical outcomes. Although not uniform, the available data suggest that PK/PD properties could be optimized by extended or continuous infusions [4–8]. On the basis of such findings, physicians could improve the therapeutic effectiveness of these drugs achieving a life-saving benefit against virulent pathogens.

Systematic reviews on the comparison between extended or continuous versus short-term infusion of

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beta-lactams [9, 10] or all antibiotics [11] have already been performed. Randomized controlled trials (RCTs) were included in these analyses, but only a few of them focused on carbapenems or piperacillin/tazobactam. One of these reviews suggested that clinical cure was higher among patients who received the same total antibiotic dose by continuous compared to those receiving short-term infusions [11]. A recent review summarized the evidence regarding the comparative effectiveness of extended or continuous versus short-term infusion of piperacillin/tazobactam but did not synthesize the available data [12].

In this context, we aimed to systematically review the published evidence regarding the impact of the duration of intravenous administration of carbapenems or piperacillin/tazobactam on clinical outcomes and synthesize the available data with the methodology of meta-analysis.

METHODS

Literature Search

A systematic search of the literature was performed in PubMed and Scopus databases in January 2012. The following search pattern was applied without a year limit: (carbapenem OR carbapenems OR meropenem OR imipenem OR “imipenem-cilastatin” OR “imipenem/cilastatin” OR doripenem OR ertapenem OR piperacillin/tazobactam) AND (extended OR prolonged OR continuous OR discontinuous OR intermittent OR short OR bolus OR intravenous) AND (duration OR infusion OR administration OR interval OR dosing). All articles were evaluated regardless of the writing language. Abstracts presented at the ICAAC and ECCMID conferences from 2005 and 2001, respectively, until present were also searched.

Study Selection

Any article reporting the comparative outcomes of patients treated with “extended or continuous” versus “short-term” infusion of a carbapenem or piperacillin/tazobactam was considered eligible for the meta-analysis. Studies reporting on the comparative outcomes of extended or continuous versus short-term duration but for different carbapenems in the 2 arms were not eligible for inclusion. Case reports and case series including <10 patients were excluded.

Data Extraction

The extracted data included the characteristics of each study (study design, country, and study period) and its patient population (number of clinically evaluable patients, infections), causative pathogens, drug regimens, and clinical outcomes (clinical cure, mortality, adverse events, and emergence of resistance) of the 2 groups of patients in each study. When the available data

of a study was considered insufficient for the analysis, the corresponding author of the study was contacted by e-mail.

Definitions and Outcomes

The primary outcomes of the review were all-cause mortality and clinical cure (as assessed by each study’s investigator) at the end of the treatment. When data regarding outcomes at the end of treatment were not provided, outcomes at test-of-cure visit were extracted. Secondary outcomes were adverse events and emergence of resistance occurring during antibiotic administration.

For the purpose of the review, patients were allocated in 2 groups: the “extended or continuous infusion” group that included patients receiving either extended infusions of a carbapenem or piperacillin/tazobactam lasting ≥ 3 hours or a 24-hour continuous infusion, and the “short-term infusion” group comprising patients receiving short-term intermittent drug regimens (ie, 20–60 minutes infusion).

Statistical Analysis

The meta-analysis was performed with Review Manager for Windows, version 5.1. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated regarding all outcomes. Statistical heterogeneity among studies was assessed by using a χ^2 test ($P < .10$ was defined to indicate significant heterogeneity) and I^2 . The Mantel-Haenszel fixed effect model (FEM) was used when there was no significant statistical heterogeneity between the studies; otherwise, the random effects model was used as appropriate.

RESULTS

The search process in both databases generated 7282 articles (PubMed 1319, Scopus 5963), of which 13 were considered eligible for the analysis [7, 13–25]. Three additional studies were identified after a search in the abstracts of ICAAC and ECCMID [15, 26, 27], and one of them was finally included [15]. The study selection process is presented in Figure 1. An RCT was excluded because it reported on piperacillin administration without tazobactam [28]. In addition, 2 other RCTs, one reporting on piperacillin/tazobactam and another on meropenem, were excluded due to the small number of included patients [29, 30]. The corresponding authors of 8 articles were contacted for the provision of additional data; 2 replied and provided the available of the requested data.

The characteristics of the eligible studies are presented in Table 1. Eight studies were retrospective [7, 14, 15, 19–21, 23, 25], 3 prospective [16, 17, 22], and 3 RCTs [13, 18, 24]. Six studies (302 patients) reported on carbapenems [15, 17, 21, 22, 24, 25], 7 (806 patients) on piperacillin/tazobactam [7, 13, 16, 18–20, 23], and 1 on both classes of antibiotics [14].

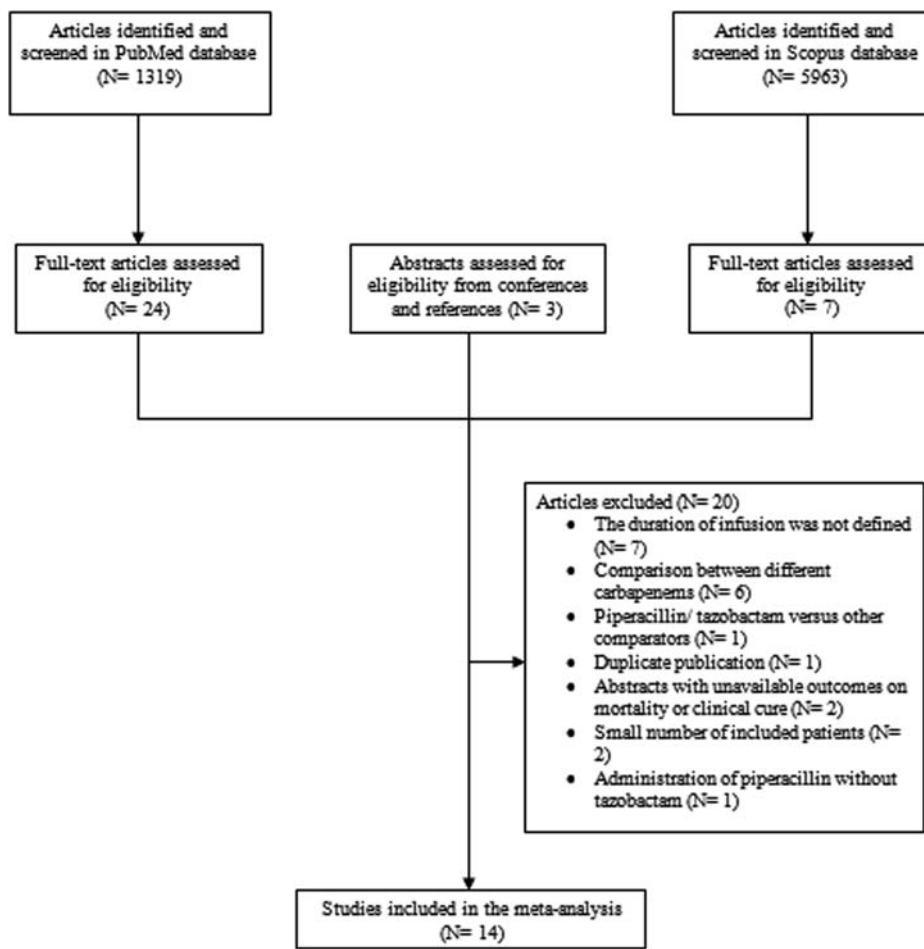


Figure 1. Flow diagram of the selection process of the included studies.

Meropenem was the most commonly administered antibiotic among studies reporting on carbapenems (in 4 of 6 studies) [17, 21, 22, 25]. Six studies evaluated patients with pneumonia [17, 20–22, 24, 25], whereas the remaining studied patients with several types of infections. In 8 of 14 studies the causative pathogens were gram-negative bacteria only [14, 15, 19–21, 23–25]; in 4 studies both gram-negative and gram-positive bacteria were included (approximately 50% each in the studies that provided more specific data) [16–18, 22]. Two studies did not provide data regarding gram staining of the causative pathogens [7, 13].

Mortality

Pooling of the outcomes of 12 studies that provided data on mortality showed that mortality was lower among patients who received extended or continuous infusions of a carbapenem or piperacillin/tazobactam than those who received short-term [Figure 2, 1116 patients, RR = 0.59 (95% CI, .41, .83)]. Publication bias was not detected. Both patients who received

continuous [Figure 2, 513 patients, RR = 0.50 (95% CI, .26, .96)] and extended infusion [Figure 2, 587 patients, RR = 0.63 (95% CI, .41, .95)] of a carbapenem or piperacillin/tazobactam had lower mortality than those receiving short-term infusions.

Six studies (782 patients) [7, 16, 18–20, 23] and 5 studies (213 patients) [15, 17, 22, 24, 25] reporting on piperacillin/tazobactam and carbapenems, respectively, provided data regarding mortality. Patients who received extended or continuous infusions of piperacillin/tazobactam had lower mortality than those receiving short-term [Figure 3, 782 patients, RR = 0.55 (95% CI, .34, .89)], whereas no significant difference in mortality was observed between the “extended or continuous” and “short-term” infusion groups of carbapenems [Figure 3, 213 patients, RR = 0.66 (95% CI, .34, 1.30)]. One study provided relevant data regarding the administration of both classes of antibiotics [14].

Two subgroup analyses regarding mortality and type of infection were performed. Patients with pneumonia (nosocomial and community acquired for whom there were available

Table 1. Characteristics and Outcomes of the Studies Included in the Meta-Analysis

Author, Year	Study Design; Years, Country	No. of Patients [Clinically Evaluable]; Infections	Bacteria	Dosage Regimen (IV)	Clinical Cure		Mortality		Adverse Events (Extended or Continuous vs Short-Term)	Emergence of Resistance
					Extended or Continuous Infusion, n/N (%)	Short-Term Infusion, n/N (%)	Extended or Continuous Infusion, n/N (%)	Short-Term Infusion, n/N (%)		
Carbapenems by extended or continuous versus short-term infusion administration										
Esterly, 2010 [15]	Retrospective; NR, USA	71 [71]; bacteremia	<i>A. baumannii</i> , <i>P. aeruginosa</i> , ESBL (+) Enterobacteriaceae	IMI/CIL or MER 3-h infusion vs IMI/CIL or MER 30-min infusion	NR	NR	12/42 (28.6)	7/29 (24.1)	NR	NR
Okimoto, 2009 [22]	Prospective; NR, Japan	50 [50]; CAP in the elderly	Gram (–) bacteria: 15 Gram (+) bacteria: 14 Unknown: 21	MER 1 g continuously vs MER 500 mg q12h 30-min infusion	20/25 (80)	19/25 (76)	0/25 (0)	0/25 (0)	5/25 (20) vs 6/25 (24)	NR
Wang, 2009 [25]	Retrospective; 2006, China	30 [30]; ICU - HAP	<i>A. baumannii</i>	MER 500 mg q6h 3-h infusion vs MER 1 g q8h 1-h infusion	15/15 (100)	15/15 (100)	0/15 (0)	0/15 (0)	NR	None
Sakka, 2007 [24]	RCT; NR, Germany	20 [20]; ICU- acquired pneumonia	Gram (–) bacilli	IMI/CIL 2/2 g continuously ^{a, b} vs IMI/CIL 1/1 g q8h 40-min infusion	NR	NR	1/10 (10)	2/10 (20)	None	NR
Itabashi, 2007 [17]	Prospective; 2004– 2005, Japan	42 [42]; severe pneumonia	Gram (–) bacteria: 10 Gram (+) bacteria: 10 Others, unknown: 34	MER 500 mg q12h 4-h infusion vs MER 500 mg q12h 1-h infusion	NR	NR	1/18 (5.6)	9/24 (37.5)	NR	NR
Lorente, 2006 [21]	Retrospective; 2002–2005, Spain	89 [89]; VAP	Gram (–) bacilli	MER 1 g continuously ^a vs MER 1 g q6h 30-min infusion	38/42 (90.5)	28/47 (59.6)	NR	NR	NR	NR
Piperacillin/tazobactam by extended or continuous versus short-term infusion administration										
Grant, 2002 [16]	Prospective; 1999– 2000, USA	98 [98]; IAIs, cSSIs, BSI, CAP, urosepsis	Gram (–)/ (+) bacteria ^d	PIP/TAZ 8/1 g or 12/ 1.5 g continuously ^a vs PIP/TAZ 3/0.375 g q6h or 4/0.5 g q8h intermittent infusion	44/47 (93.6)	42/51 (82.4)	0/47 (0)	5/51 (9.8)	None	2 isolates ^c
Buck, 2005 [13]	RCT, non-blinded; NR, Germany	24 [24]; community- or hospital- acquired infections	NR	PIP/TAZ 8/1 g continuously ^a vs PIP/TAZ 4/0.5 g q8h intermittent infusion	8/12 (66.7)	8/12 (66.7)	NR	NR	NR	NR

Table 1 continued.

Author, Year	Study Design; Years, Country	No. of Patients [Clinically Evaluable]; Infections	Bacteria	Dosage Regimen (IV)	Clinical Cure		Mortality		Adverse Events (Extended or Continuous vs Short-Term)	Emergence of Resistance
					Extended or Continuous Infusion, n/N (%)	Short-Term Infusion, n/N (%)	Extended or Continuous Infusion, n/N (%)	Short-Term Infusion, n/N (%)		
Lau, 2006 [18]	MC RCT, non- blinded; 2002– 2004, USA	262 [167]; cIAIs	Gram (–)/ (+) bacteria ^d	PIP/TAZ 12/1.5 g continuously ^a vs PIP/TAZ 3/0.375 g q6h 30-min infusion	70/81 (86.4)	76/86 (88.4)	1/130 (0.8)	3/132 (2.3)	22/130 (16.9) vs 18/132 (13.6)	None
Lodise, 2007 [19]	Retrospective; 2000–2004, USA	194 [194]; <i>P. aeruginosa</i> infections	<i>P. aeruginosa</i>	PIP/TAZ 3/0.375 g q8h 4-h infusion vs PIP/TAZ 3/0.375 g q4h or q6h 30-min infusion	NR	NR	9/102 (8.8)	14/92 (15.2)	NR	NR
Lorente, 2009 [20]	Retrospective; 2002–2007, Spain	83 [83]; VAP	Gram (–) bacilli	PIP/TAZ 4/0.5 g continuously ^a vs PIP/TAZ 4/0.5 g q6h 30-min infusion	33/37 (89.2)	26/46 (56.5)	8/37 (21.6)	14/46 (30.4)	NR	None
Patel, 2009 [23]	Retrospective; NR, USA	129 [129]; mainly urinary and respiratory tract infections	Gram (–) bacteria	PIP/TAZ 3/0.375 g q8h 4-h infusion vs PIP/TAZ 3/0.375 g to 4/0.5 g q6h or q8h 30-min infusion	NR	NR	4/70 (5.7)	5/59 (8.5)	NR	NR
Roberts, 2010 [7]	Retrospective; 2005, Australia	16 [16]; ICU sepsis	NR	PIP/TAZ 12/1.5 g continuously ^a vs PIP/TAZ 4/0.5 g q6h or q8h 20-min infusion	8/8 (100)	8/8 (100)	0/8 (0)	0/8 (0)	None	None
Carbapenems or piperacillin/tazobactam by extended or continuous versus short-term infusion administration										
Dow, 2011 [14]	Retrospective; 2008–2009, USA	121 [121]; ICU infections	Gram (–) bacteria	PIP/TAZ 3/0.375 g q8h or MER 500 mg q6h 3or 4-h infusion vs PIP/TAZ 3/0.375 g q6h or MER 500 mg q6h 30-min infusion	NR	NR	8/67 (11.9)	11/54 (20.4)	NR	NR

Abbreviations: BSI, bloodstream infection; CAP, community-acquired pneumonia; cSSIs, complicated skin and soft-tissue infections; ESBL, extended spectrum beta lactamase; HAP, hospital-acquired pneumonia; IAIs, intra-abdominal infections; ICU, intensive care unit; IMI/CIL, imipenem/cilastatin; IV, intravenous; MC, multicenter; MER, meropenem; NR, not reported; RCT, randomized controlled trial; PIP/TAZ, piperacillin/tazobactam; VAP, ventilator-associated pneumonia.

^a A loading dose was administered before continuous infusion.

^b IMI/CIL 1 g/1 g q8h was administered after the first 3 days.

^c The resistant isolates occurred in the continuous infusion group.

^d No. of isolates in each group was not available.

^e PIP/TAZ 8 g/1 g was administered the first day.

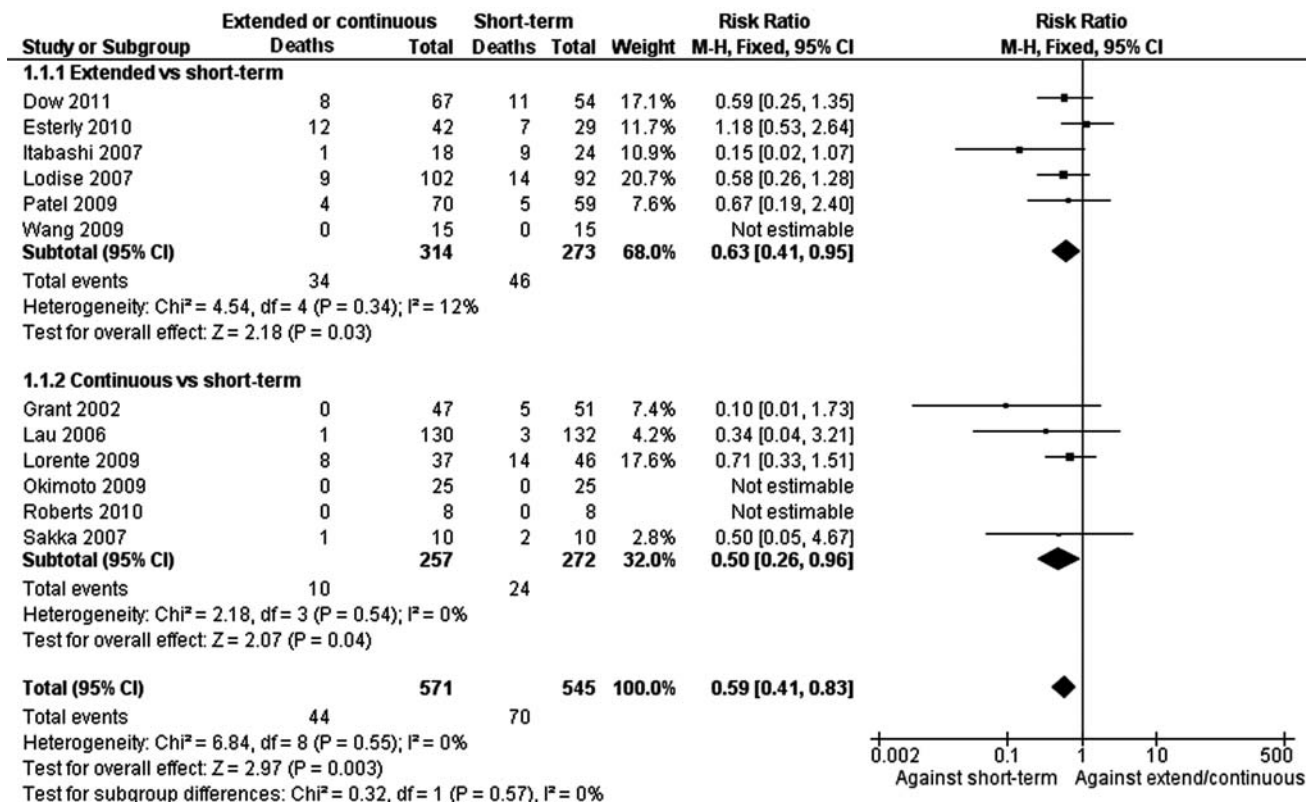


Figure 2. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, “no difference” point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

separate data) who received extended or continuous infusions of carbapenems or piperacillin/tazobactam had lower mortality than those receiving short-term infusion [225 patients, RR = 0.50 (95% CI, .26, .96)]. Mortality was also lower for patients whose infections could not be specified when extended or continuous infusions of carbapenems or piperacillin/tazobactam were used [891 patients, RR = 0.63 (95% CI, .41, .95)].

Clinical Cure

Pooling of the outcomes of 8 studies showed that there was no statistical difference regarding clinical cure between patients receiving extended or continuous and short-term infusions [Figure 4, 557 patients, RR = 1.13 (95% CI, .99, 1.28)]. Publication bias was detected in the analysis of clinical cure. No difference was observed between continuous and short-term group with regard to clinical cure [527 patients, RR = 1.16 (95% CI, .99, 1.35)]. In the extended group only 1 study provided data regarding clinical cure [25]. Three studies (169 patients) [21, 22, 25] and 5 studies (388 patients) [7, 13, 16, 18, 20] reporting on carbapenems and piperacillin/tazobactam provided data regarding clinical cure, respectively. Patients who received extended or continuous infusions of piperacillin/

tazobactam [388 patients, RR = 1.11 (95% CI, .95, 1.31)] or carbapenems [169 patients, RR = 1.16 (95% CI, .82, 1.65)] had similar clinical cure with the “short-term” group.

Adverse Events

Five studies in total provided data regarding adverse events that occurred during treatment [7, 16, 18, 22, 24]. In 3 of them no adverse events were reported [7, 16, 24]. Five of 25 patients (20%) in the continuous group experienced adverse events, whereas 6 of 25 (24%) in the short-term group in a study reporting on carbapenems experienced them [22]. Abnormalities in the liver and kidney function tests were only reported in this study. Last, 22 of 130 patients (16.9%) in the continuous group experienced adverse events, whereas 18 of 132 (13.6%) in the short-term group in a study reporting on piperacillin/tazobactam experienced them [18]. Gastrointestinal disorders and infections were the most commonly reported adverse effects, followed by electrolyte disturbances and nervous system disorders. No significant differences between the 2 treatment groups were observed for each of the aforementioned adverse events. Serious adverse events (*Clostridium difficile* colitis, renal failure, confusion, tachycardia, and a

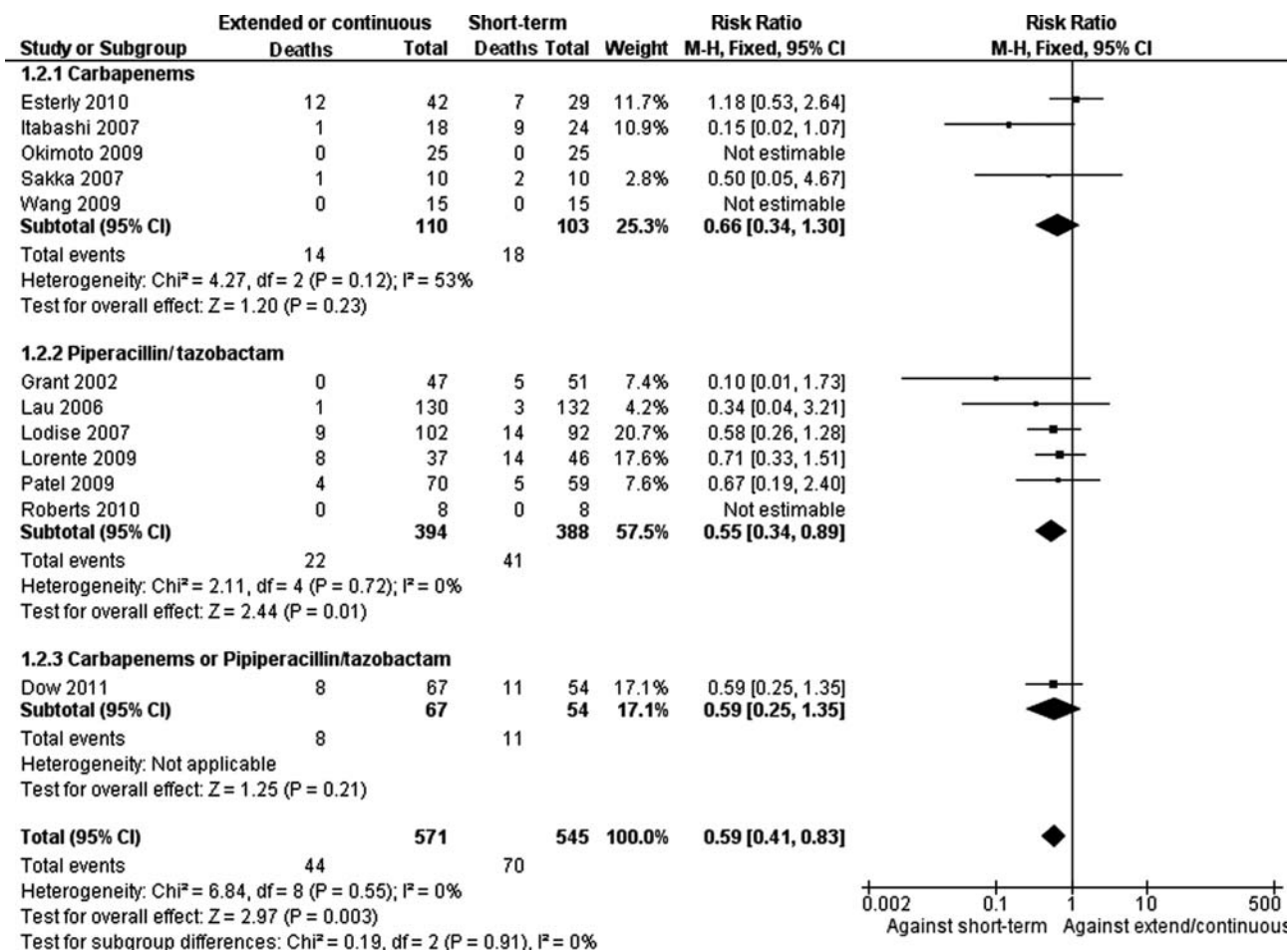


Figure 3. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by the administered antibiotics. Vertical line, “no difference” point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

tonic/clonic seizure) were reported only in the continuous group, but none was associated with death.

Emergence of Resistance

Five studies provided data regarding emergence of resistance during treatment [7, 16, 18, 20, 25]. In 4 of them resistant strains were not isolated following the initiation of treatment [7, 18, 20, 25]. In 1 study, 2 isolates in the continuous group developed resistance to piperacillin/tazobactam during treatment [16]. The studies did not provide data regarding the time point this outcome was assessed, the culture sample (surveillance or clinical), or the species of resistant pathogens.

DISCUSSION

The findings of this meta-analysis suggest that in total, extended or continuous infusion of a carbapenem or piperacillin/

tazobactam resulted in lower mortality than short-term infusion. Patients who received extended or continuous infusion of piperacillin/tazobactam had lower mortality than those receiving short-term infusion; no significant difference regarding mortality was observed for patients receiving carbapenems. Extended and continuous infusion separately resulted in lower mortality than short-term infusion. Both patients with pneumonia and those with infections in different body sites had lower mortality with extended or continuous infusions than with short-term infusion.

To our knowledge, this is the first meta-analysis that showed a reduction in mortality in patients with moderate to severe infections using an alternative mode of antibiotic infusion. Meta-analyses performed in the past did not show similar benefits [9–11]. This can be attributed to the antibiotics that were evaluated in the included studies of each analysis (mainly cephalosporins and aminoglycosides in other

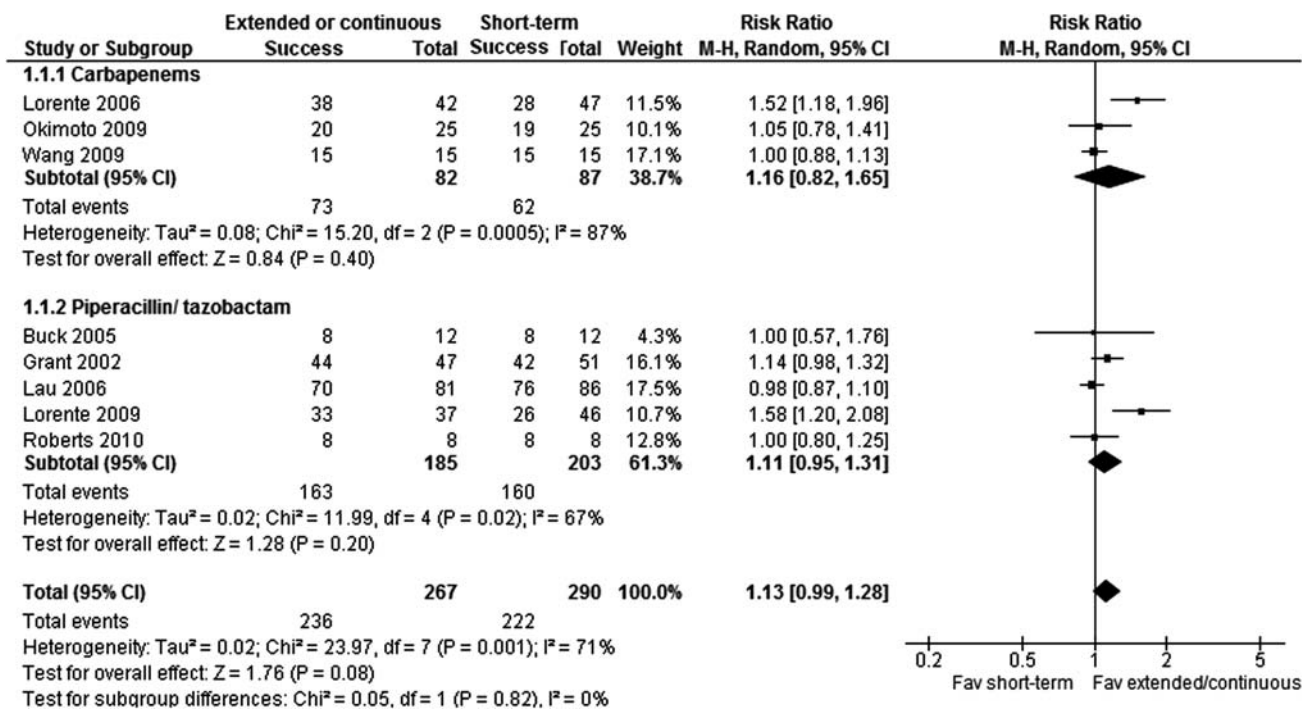


Figure 4. Forest plot depicting the risk ratios of clinical cure of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, “no difference” point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

analyses, carbapenems and piperacillin/tazobactam only in the current one) that display different PK/PD properties and antimicrobial spectrum. Additional factors include the different patient populations under study, different infections or severity of infections, and different study design. In addition, although RCTs and meta-analyses did not show a difference in mortality or even in clinical cure, when individual newer or older antibiotics were compared, a difference in mortality was found in this analysis when the duration of infusion was prolonged. A retrospective study comparing the extended infusion of piperacillin/tazobactam and short-term infusion of several different antibiotics (including piperacillin/tazobactam) also showed lower mortality in the extended infusion group [31].

Besides the mode of the administration, the total daily dose adjusted for body weight and creatinine clearance are additional important factors contributing to the outcome of patients. Previously published reports showed that in severely ill patients both the dose and the mode of administration can positively affect the outcome of patients [32, 33]. In addition, the severity of the underlying infection (represented as severity scores), the MIC of the isolated pathogens and the timing of antibiotic administration also contribute significantly in patients' outcome. It should be mentioned that one of the included studies showed that patients receiving the extended infusion of piperacillin/

tazobactam had lower mortality than patients in the short-term infusion when the APACHE II score was ≥ 17 ($P = .04$); however, no such difference was noted in patients with APACHE II score < 17 [19]. Data regarding such variables was not available in the other included studies.

It is noteworthy that although mortality was significantly lower in patients who received extended or continuous infusions, the difference in clinical cure between the 2 groups did not reach statistical significance. This could be attributed to the smaller sample size in the clinical cure comparison. In addition, the observed statistical heterogeneity in the meta-analysis of clinical cure was substantial to considerable, whereas no statistical heterogeneity was found in the analysis of mortality. As it is shown in Figures 2 and 3, the trend of all but one of the included studies in the analysis of mortality was toward lower mortality for patients receiving extended or continuous infusion of the studied antibiotics. Another issue that should be taken into consideration is that clinical cure is a more subjective outcome than death, especially when the decision on cure or failure is taken retrospectively. We have noticed similar findings in meta-analyses published in the past [34–36].

Carbapenems as well as piperacillin/tazobactam are time-dependent antibiotics in which the time the concentration of

the antibiotic remains above the MIC of the pathogen ($T > MIC$) is the pharmacodynamic parameter associated with effectiveness. For carbapenems the $T > MIC$ required for the achievement of the bactericidal activity is 40% of their dosing interval, whereas that for piperacillin/tazobactam is 50% [37]. Studies on patients that evaluated the PK/PD properties of carbapenems suggested that their blood concentration is better maintained above the MIC via extended or continuous than short-term infusion [4, 8]. Likewise, Monte Carlo simulations [38–40] and studies on healthy volunteers [41, 42] have reported that the extended or continuous duration administration of carbapenems results in better PK/PD outcomes, namely, $T > MIC$ and probability of target attainment. Similar findings had been reported for extended infusions of piperacillin/tazobactam [5–7, 12, 28, 43].

Carbapenems as well as piperacillin/tazobactam are, in general, well-tolerated antibiotics [44, 45]. There is limited data regarding the adverse events among patients treated with extended or continuous duration infusion of antibiotics. The 2 studies that provided data did not find any differences between the compared groups (extended or continuous versus short-term infusion) of patients. One could claim that the nonstandard prolonged infusion of these drugs could induce further toxicity reactions due to the longer time the drug's concentration remains high within tissues. It is noteworthy that serious adverse events were reported only for patients receiving continuous piperacillin/tazobactam in 1 study [18]. On the other hand, a lower total daily dose may be required for the extended or continuous infusion, because lower dose of the drug is required to achieve similar concentrations in blood or other sites, as was reported elsewhere [46, 47]. Whether extended or continuous duration of administration is associated or not with adverse events requires further study.

The emergence of resistance during the antimicrobial treatment is a serious problem occurring when the tissue drug concentration is below the MIC of the pathogen, probably due to suboptimal doses [48]; reviews suggested that optimization of the dosing scheme could be one of the potential strategies to overcome development of resistance [35]. For example, imipenem monotherapy for *P. aeruginosa* infections has been associated with the emergence of resistance during therapy [49]. In this meta-analysis, only 2 strains that developed resistance during treatment were reported [16]. Four studies reported that no resistant pathogen was observed during treatment [7, 18, 20, 25]. In short-term infusions, the interval during which the blood concentration of the drug is above the MIC of the pathogen is shorter than in prolonged infusion, thus allowing bacteria to survive and develop resistance mechanisms. The theoretical advantage of extended or continuous duration of infusion on the development of resistance requires further study.

The extended or continuous infusion of an antibiotic may also have economic benefits. Studies suggested that extended or continuous infusion of carbapenems and piperacillin/tazobactam was more cost-effective than short-term infusion [13, 16, 25, 50]. The potential economic benefits might be attributed to lower cost for antibiotic acquisition as showed in studies that used lower doses in patients with extended infusion or fewer days of ICU or hospital stay [14, 25].

The findings of this meta-analysis should be interpreted in view of certain limitations. First, 3 of 14 of the included studies were RCTs; thus, RCTs contributed only a small subset of patients in the meta-analysis (approximately 25%). Therefore, there is a possibility that confounding factors that could not be tested have contributed significantly in the outcomes of patients. Second, other antibiotics have been administered in several of the enrolled patients [13, 19–21, 23]. The outcome of patients treated with monotherapy and combination therapy was not available for further analysis. Although differences in favor of combination therapy for the treatment of patients with *P. aeruginosa* have been implied in a meta-analysis [51], the currently available data suggest that combination antibiotic therapy is not associated with better outcomes than monotherapy [52–56]. In everyday clinical practice, most patients with severe infections receive a combination of antibiotics. In addition, it is unlikely that an adequately powered RCT will evaluate the outcome of patients with either severe or multidrug-resistant infection with monotherapy or combination therapy in the near future. Third, in a few studies (those reporting on extended infusions) the total daily dose of the administered antibiotic was different in the compared groups or low for the short-term infusions, thus providing an additional confounding factor as to whether the clinical outcome should be attributed to the duration of the infusion or the total daily dose [14, 19, 23, 25].

In conclusion, the evidence from mainly nonrandomized studies suggests that the extended or continuous infusion of carbapenems and piperacillin/tazobactam results in lower mortality, a finding that applies for both continuous and extended infusion separately. However, well-designed RCTs are warranted to validate these findings before such strategy can be widely applied in clinical practice. In addition, studies should focus on patient populations that might benefit more, should address the issues of antibiotic resistance and adverse events, and provide insights on the economic variables.

Note

Potential conflicts of interest. M. E. F. has participated in advisory boards of Pfizer, Astellas, and Bayer and has received lecture honoraria from Merck, Pfizer, AstraZeneca, Astellas, Cipla, Novartis, and Glenmark. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Baughman RP. The use of carbapenems in the treatment of serious infections. *J Intensive Care Med* **2009**; 24:230–41.
2. Michalopoulos A, Falagas ME. Treatment of *Acinetobacter* infections. *Expert Opin Pharmacother* **2012**; 11:779–88.
3. Thiem U, Heppner HJ, Pientka L. Elderly patients with community-acquired pneumonia: optimal treatment strategies. *Drugs Aging* **2011**; 28:519–37.
4. Jaruratanasirikul S, Sriwiriyan S, Punyo J. Comparison of the pharmacodynamics of meropenem in patients with ventilator-associated pneumonia following administration by 3-hour infusion or bolus injection. *Antimicrob Agents Chemother* **2005**; 49:1337–9.
5. Li C, Kuti JL, Nightingale CH, Mansfield DL, Dana A, Nicolau DP. Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection. *J Antimicrob Chemother* **2005**; 56:388–95.
6. Lodise TP Jr, Lomaestro B, Rodvold KA, Danziger LH, Drusano GL. Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation. *Antimicrob Agents Chemother* **2004**; 48:4718–24.
7. Roberts JA, Kirkpatrick CM, Roberts MS, Dalley AJ, Lipman J. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. *Int J Antimicrob Agents* **2010**; 35:156–63.
8. Thalhammer F, Traunmuller F, El Menyawi I, et al. Continuous infusion versus intermittent administration of meropenem in critically ill patients. *J Antimicrob Chemother* **1999**; 43:523–7.
9. Roberts JA, Webb S, Paterson D, Ho KM, Lipman J. A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. *Crit Care Med* **2009**; 37:2071–8.
10. Tamma PD, Putcha N, Suh YD, Van Arendonk KJ, Rinke ML. Does prolonged beta-lactam infusion improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. *BMC Infect Dis* **2011**; 11:181.
11. Kasiakou SK, Sermades GJ, Michalopoulos A, Soteriades ES, Falagas ME. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. *Lancet Infect Dis* **2005**; 5:581–9.
12. Mah GT, Mabasa VH, Chow I, Ensom MH. Evaluating outcomes associated with alternative dosing strategies for piperacillin/tazobactam: a qualitative systematic review. *Ann Pharmacother* **2012**; 46:265–75.
13. Buck C, Bertram N, Ackermann T, Sauerbruch T, Derendorf H, Paar WD. Pharmacokinetics of piperacillin-tazobactam: intermittent dosing versus continuous infusion. *Int J Antimicrob Agents* **2005**; 25:62–7.
14. Dow RJ, Rose WE, Fox BC, Thorpe JM, Fish JT. 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* **2011**; 19:413–7.
15. Esterly J, Gilley J, Steadman E, Postelnick M, Scheetz MH. Clinical Outcomes of Subjects Receiving Carbapenems for Gram Negative Blood Stream Infections according to Carbapenem MIC. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), **2010**.
16. Grant EM, Kuti JL, Nicolau DP, Nightingale C, Quintilliani R. Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital. *Pharmacotherapy* **2002**; 22:471–83.
17. Itabashi S. Clinical efficacy of prolonged (4 hour) drip infusion of meropenem against severe pneumonia. *Japan J Antibiot* **2007**; 60:161–70.
18. Lau WK, Mercer D, Itani KM, et al. 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* **2006**; 50:3556–61.
19. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis* **2007**; 44:357–63.
20. Lorente L, Jimenez A, Martin MM, Iribarren JL, Jimenez JJ, Mora ML. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. *Int J Antimicrob Agents* **2009**; 33:464–8.
21. Lorente L, Lorenzo L, Martin MM, Jimenez A, Mora ML. Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to gram-negative bacilli. *Ann Pharmacother* **2006**; 40:219–23.
22. Okimoto N, Ishiga M, Nanba F, et al. Clinical effects of continuous infusion and intermittent infusion of meropenem on bacterial pneumonia in the elderly. *Nihon Kokyuki Gakkai Zasshi* **2009**; 47:553–7.
23. Patel GW, Patel N, Lat A, et al. Outcomes of extended infusion piperacillin/tazobactam for documented gram-negative infections. *Diagn Microbiol Infect Dis* **2009**; 64:236–40.
24. Sakka SG, Glauner AK, Bulitta JB, et al. 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* **2007**; 51:3304–10.
25. Wang D. Experience with extended-infusion meropenem in the management of ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii*. *Int J Antimicrob Agents* **2009**; 33:290–1.
26. Lee W, Cao JY, Ong S, Chan K, Kwa A. A Prospective Observational Study of the Clinical Efficacy and Safety of Bolus versus Extended-Infusions of Meropenem in Critically Ill Patients with Gram-Negative Pneumonia. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), **2009**.
27. Schiller DS, Rezaei F, Meadows M, et al. Four-Hour Infusions of Piperacillin-Tazobactam Improve Outcomes in Critically Ill Patients. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), **2010**.
28. Rafati MR, Rouini MR, Mojtahedzadeh M, et al. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. *Int J Antimicrob Agents* **2006**; 28:122–7.
29. Kojima M, Sato N, Hakozaiki M, et al. A preliminary study of the administration of carbapenem antibiotics in sepsis patients on the basis of the administration time. *Jpn J Antibiot* **2005**; 58:452–7.
30. Pedeboscq S, Dubau B, Frappier S, et al. Comparison of 2 administration protocols (continuous or discontinuous) of a time-dependent antibiotic, Tazocin. *Pathol Biol (Paris)* **2001**; 49:540–7.
31. Yost RJ, Cappelletty DM. The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) study: a multicenter study. *Pharmacotherapy* **2011**; 31:767–75.
32. Falagas ME, Siempos II, Tsakoumis I. Cure of persistent, post-appendectomy *Klebsiella pneumoniae* septicemia with continuous intravenous administration of meropenem. *Scand J Infect Dis* **2006**; 38:807–10.
33. Taccone FS, Cotton F, Roisin S, Vincent JL, Jacobs F. Optimal meropenem concentrations to treat multi-drug resistant *Pseudomonas aeruginosa* septic shock. *Antimicrob Agents Chemother* **2012**; 56:2129–31.
34. Paul M, Yahav D, Bivas A, Fraser A, Leibovici L. Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. *Cochrane Database Syst Rev* **2010**; 11:CD005197.
35. Siempos II, Vardakas KZ, Manta KG, Falagas ME. Carbapenems for the treatment of immunocompetent adult patients with nosocomial pneumonia. *Eur Respir J* **2007**; 29:548–60.

36. Vardakas KZ, Mavros MN, Roussos N, Falagas ME. Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: focus on the study design. *Mayo Clinic Proceedings* **2012**; 87:349–63.
37. Drusano GL. Prevention of resistance: a goal for dose selection for antimicrobial agents. *Clin Infect Dis* **2003**; 36:S42–50.
38. Kim A, Kuti JL, Nicolau DP. Probability of pharmacodynamic target attainment with standard and prolonged-infusion antibiotic regimens for empiric therapy in adults with hospital-acquired pneumonia. *Clin Ther* **2009**; 31:2765–78.
39. Lee LS, Kinzig-Schippers M, Nafziger AN, et al. Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. *Diagn Microbiol Infect Dis* **2010**; 68:251–8.
40. Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. *J Antimicrob Chemother* **2009**; 64:142–50.
41. Kikuchi E, Kikuchi J, Nasuhara Y, Oizumi S, Ishizaka A, Nishimura M. Comparison of the pharmacodynamics of biapenem in bronchial epithelial lining fluid in healthy volunteers given half-hour and three-hour intravenous infusions. *Antimicrob Agents Chemother* **2009**; 53:2799–803.
42. Krueger WA, Bulitta J, Kinzig-Schippers M, et al. Evaluation by Monte Carlo simulation of the pharmacokinetics of two doses of meropenem administered intermittently or as a continuous infusion in healthy volunteers. *Antimicrob Agents Chemother* **2005**; 49:1881–9.
43. Goncalves-Pereira J, Povoas P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. *Crit Care* **2011**; 15:R206.
44. Gin A, Dilay L, Karlowsky JA, Walkty A, Rubinstein E, Zhanel GG. Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. *Expert Rev Anti Infect Ther* **2007**; 5:365–83.
45. Nicolau DP. Carbapenems: a potent class of antibiotics. *Expert Opin Pharmacother* **2008**; 9:23–37.
46. Perrott J, Mabasa VH, Ensom MH. Comparing outcomes of meropenem administration strategies based on pharmacokinetic and pharmacodynamic principles: a qualitative systematic review. *Ann Pharmacother* **2010**; 44:557–64.
47. Roberts JA, Paratz J, Paratz E, Krueger WA, Lipman J. Continuous infusion of beta-lactam antibiotics in severe infections: a review of its role. *Int J Antimicrob Agents* **2007**; 30:11–8.
48. Peterson LR. Squeezing the antibiotic balloon: the impact of antimicrobial classes on emerging resistance. *Clin Microbiol Infect* **2005**; 11 (Suppl 5):4–16.
49. Zanetti G, Bally F, Greub G, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* **2003**; 47:3442–7.
50. Florea NR, Kotapati S, Kuti JL, Geissler EC, Nightingale CH, Nicolau DP. Cost analysis of continuous versus intermittent infusion of piperacillin-tazobactam: a time-motion study. *Am J Health Syst Pharm* **2003**; 60:2321–7.
51. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* **2004**; 4:519–27.
52. Bliziotis IA, Petrosillo N, Michalopoulos A, Samonis G, Falagas ME. Impact of definitive therapy with beta-lactam monotherapy or combination with an aminoglycoside or a quinolone for *Pseudomonas aeruginosa* bacteremia. *PLoS One* **2011**; 6:e26470.
53. Furno P, Bucaneve G, Del Favero A. Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis. *Lancet Infect Dis* **2002**; 2:231–42.
54. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ* **2004**; 328:668.
55. Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* **2006**; 57: 176–89.
56. Traugott KA, Echevarria K, Maxwell P, Green K, Lewis JS 2nd. Monotherapy or combination therapy? The *Pseudomonas aeruginosa* conundrum. *Pharmacotherapy* **2011**; 31:598–608.