Saving Lives With Optimal Antimicrobial Chemotherapy

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(See the Major Article by Dulhunty et al, on pages 236–44, and the Invited Article by Falagas et al, on pages 272–82.)

Keywords. β-lactams; chemotherapy; pharmacodynamics; meta-analysis.

The introduction of antimicrobial chemotherapy was an unprecedented advance in the practice of medicine. Previously fatal infections became treatable and antimicrobials were the agents of that salvage of life. In the more modern era, these agents also became the drugs that were permissive for many of the other modern medical miracles that we currently enjoy. The ability to treat serious infections in neutropenic cancer patients allowed the use of intensive oncologic chemotherapy. In the same vein, immunosuppressive therapy for organ and bone marrow transplants are made possible by antimicrobial therapy, as has the routine use of interventions that cross natural anatomic boundaries.

In the early days of antimicrobial therapy, pioneers such as Harry Eagle recognized that certain administration profiles of drug prompted better therapeutic effect. This was demonstrated in a landmark paper published in the *New England Journal of Medicine* [1]. Certain agents such as penicillin had a better therapeutic effect when administered on very short administration intervals, whereas drugs such as the tetracyclines had antimicrobial effects that were somewhat independent of administration schedule. Unfortunately much of this information became lost in the 1960s and 1970s.

In the late 1980s and early 1990s, these principles were rediscovered by the laboratory of William Craig [2–4]. These studies linked the effect of different antimicrobial classes, doses, and schedules to the reduction in colony-forming units (CFUs) in murine thigh or pneumonia models. Shortly thereafter, the burgeoning science of pharmacodynamics and pharmacometrics allowed identification of relationships between drug exposure indexed to the minimum inhibitory concentration (MIC) of the infecting pathogen and clinical and/or microbiological outcomes [5–7]. The first study was a retrospective evaluation, but the last 2 were prospectively designed with analysis plans filed with the Food and Drug Administration (FDA). Such studies demonstrated conclusively that it was relatively straightforward to derive exposure-response relationships in the midst of clinical trials, employing a number of different mathematical techniques.

The next step was to demonstrate the link between the animal model findings and the clinical trial pharmacodynamics relationships. Ambrose and colleagues [8] examined outcomes from clinical trials relative to the effect breakpoints determined from murine pharmacodynamic studies. They demonstrated a strong concordance between the preclinical and clinical pharmacodynamic studies for a number of different antimicrobial classes. Consequently, we can say that another brick was laid in the edifice of antimicrobial dynamics.

While these data are convincing, it is also important to demonstrate that attainment of the "correct" antimicrobial targets has an impact on endpoints other than traditional clinical and microbiological outcomes in "real world" clinical practice settings. The clinical benefits of prolonged β-lactam infusion among critically ill patients were highlighted by the study performed at Albany Medical Center Hospital by Lodise and colleagues. Based on the results of a Monte Carlo simulation, prolonged infusion of piperacillin-tazobactam (3.375 g administered over a 4-hour period every 8 hours) was adopted as the standard hospital-wide piperacillin-tazobactam dosing scheme at their institution in February 2002. To evaluate the real-world effectiveness of this automatic dose substitution program, 14-day mortality and hospital length of stay after culture collection were

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compared among patients with documented piperacillin-tazobactam-susceptible *Pseudomonas aeruginosa* infections who received intermittent infusions of this agent (2000–2002) prior to the switch or prolonged piperacillin-tazobactam infusion (2002–2004) after implementation of the dose substitution program. Overall, there were significantly fewer deaths and significantly shorter lengths of stay for seriously ill patients (APACHE II score, ≥17). These findings were recapitulated [9] in a recent multicenter retrospective comparative evaluation of critically ill patients who received prolonged or intermittent infusions of piperacillin-tazobactam. In this study of critically ill patients infected with a broad range of gram-negative causative pathogens, extended infusion of piperacillin-tazobactam was found to prolong survival 3 days on average and considerably reduced the risk of mortality. More recently, Scaglione et al prospectively studied patients with hospital-acquired pneumonia receiving a wider range of antibiotics. He demonstrated that dose optimization through feedback control significantly altered both survivorship and length of stay [10]. This study included β-lactams. Dose alteration occurred if the measured drug concentration was less than the MIC of the infecting pathogen; the drug concentration was checked at 70% of the dosing interval.

The theory set forth in preclinical model systems, combined with Monte Carlo simulation, was upheld in these evaluations. The drawback is that both evaluations were retrospective [9, 11], and the Scaglione study used patients who did not have both an MIC measurement and a plasma concentration measurement as the control group [10]. In this issue of *Clinical Infectious Diseases,* there are 2 sets of observations: one is a meta-analysis of continuous infusion or extended infusion compared with short-term infusions of β-lactams and the other is a randomized, double-blind, double-dummy evaluation of continuous infusion versus intermittent infusion of β-lactams. While previous meta-analyses of randomized clinical trials (RCTs) did not conclude there were any clinical benefits in extending the infusion duration of β-lactams [12–14], the meta-analysis by Falagas et al [15], comprising mainly observational studies, found mortality to be significantly lower among patients receiving extended or continuous infusion of carbapenems or piperacillin-tazobactam compared with those receiving short-term infusions (relative risk, 0.59; 95% confidence interval, 0.41–0.83), and this difference in mortality was most pronounced in patients with pneumonia (relative risk, 0.50; 95% confidence interval, 0.26–0.96).

Beyond differences in antibiotics studied in the included studies (only a few RCTs focused on carbapenems or piperacillin-tazobactam), there are several possible explanations for the discordance in results between the Falagas et al and "RCT" meta-analyses [12–14]. Disease severity in the studies included in the RCT meta-analysis was generally low, as evidenced by low mortality rates in the majority of studies. In addition, diverse groups of patients and infection types were included in the RCTs and a higher antibiotic dose was used in the intermittent administration group in most studies included in the RCT meta-analyses. In contrast, the studies included in the meta-analysis by Falagas et al [15] largely comprised critically ill patients with nosocomial infections, namely pneumonia, receiving comparable dosing regimens. Collectively, the null result from the RCT meta-analyses and positive data from the observational studies meta-analysis suggest that prolonged or continuous infusion of β-lactams is unlikely to be advantageous for all hospitalized patient populations, but may be beneficial for specific groups, such as critically ill patients with higher MIC pathogens. This was demonstrated clearly by the Lodise study [11], where benefit from prolonged infusion only occurred in patients with APACHE II scores of ≥17, and was also seen in the study by Yost and colleagues [9], where all patients were in the intensive care unit (ICU).

The finding of lack of difference between prolonged and intermittent dosing on outcomes of patients who are not seriously infected should not come as a surprise. Recently, it has been demonstrated [16, 17] that the ability of granulocytes to kill invading bacteria is a saturable process. With relatively low bacterial burdens, granulocytes can reduce counts by 1–2 $\log_{10}$ CFUs/g/day. As counts meet and exceed the burdens seen in infections such as nosocomial pneumonia, the ability to prevent outgrowth of the infecting bacterium is lost. Consequently, the adequacy of the antimicrobial regimen becomes paramount in these types of infectious conditions. With seriously ill patients with dense bacterial burdens, the antibiotic regimen must have an impact which will render the burden less than the saturation point of granulocytes, allowing ultimate successful treatment of the patient. With lesser burdens, the antimicrobial regimen needs to do little, as the host defenses, especially the granulocytes, participate to drive a good outcome. An example is seen in the oral cephalosporins, for which FDA claims were granted for community-acquired pneumonia. The majority of these patients, had they had a PORT score, would undoubtedly have had scores of 1 and 2, with relatively low bacterial burdens. The antibiotic need only achieve stasis in order to allow the granulocytes to achieve the cell kill required to drive a good outcome.

As an important first step in delineating the outcomes associated with intermittent infusion relative to continuous infusion in infected, critically ill patients, Dulhunty et al conducted a small-scale, prospective, double-dummy, randomized controlled trial of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem, and ticarcillin-clavulanate in 5 ICUs across Australia and Hong Kong [18].

The primary endpoint of this study was in achieving free-drug concentrations above the MIC of the infecting pathogen for the entire dosing interval. Indeed, the superiority of continuous infusion was directly demonstrated for this endpoint; antibiotic concentrations were in excess of the MIC in 18 (82%) of 22 patients in the continuous arm versus 6 (29%) of 21 patients in the short-infusion arm ($P = .001$). They were also able to demonstrate that continuous infusion of β-lactam antibiotics results in higher rates of clinical cure compared with intermittent administration in these critically ill patients (clinical cure at 7–14 days after study drug cessation was 27% higher [70% vs 43%] in the continuous infusion group relative to the intermittent dosing group, and this finding persisted even after adjusting for therapy changes; $P = .037$). It should be noted that the study was only powered for the endpoint of maintaining free-drug concentration above the MIC for the entire dosing interval. Nonetheless, other endpoints such as ICU-free days and mortality, while not achieving statistical significance (19.5 days vs 17 days and 90% vs 80% for continuous vs intermittent infusion), each showed a trend in favor of continuous infusion. The positive findings from this study provide strong rationale for further multicenter trials with sufficient power to delineate differences in outcomes such as clinical and microbiological outcome as well as mortality and length of stay. Indeed, Dulhunty and colleagues [18] have pointed out that previous authors [19] have shown the way to employ smaller but well-focused clinical trials such as the one in this issue of *Clinical Infectious Diseases* as a means of optimizing the design of larger randomized trials and also providing reasonable power estimates for those trials for endpoints of interest.

The papers of Falagas et al [15] and Dulhunty et al [18] are important steps forward. We have seen the progression of evidence for optimizing antimicrobial chemotherapy from in vitro and animal model data through to retrospective examinations of clinical data. Here, we have a well-done meta-analysis that is concordant with previous preclinical data. We also have a prospective randomized double-blind, double-dummy clinical trial focused in ICU patients that had a positive outcome for its primary endpoint, but also demonstrated a significant improvement in clinical outcome. We must eagerly await the final capstone of a prospective multicentered, randomized trial powered for outcomes such as clinical or microbiological outcome, length of stay, and perhaps mortality.

Note

Potential conflicts of interest. All authors: No reported 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.

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MAJOR ARTICLE

Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

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(See the Editorial Commentary by Drusano and Lodise, on pages 245–7, and the Invited Article by Falagas et al, on pages 272–82.)

Background. Beta-lactam antibiotics are a commonly used treatment for severe sepsis, with intermittent bolus dosing standard therapy, despite a strong theoretical rationale for continuous administration. The aim of this trial was to determine the clinical and pharmacokinetic differences between continuous and intermittent dosing in patients with severe sepsis.

Methods. This was a prospective, double-blind, randomized controlled trial of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem, and ticarcillin-clavulanate conducted in 5 intensive care units across Australia and Hong Kong. The primary pharmacokinetic outcome on treatment analysis was plasma antibiotic concentration above the minimum inhibitory concentration (MIC) on days 3 and 4. The assessed clinical outcomes were clinical response 7–14 days after study drug cessation, ICU-free days at day 28 and hospital survival.

Results. Sixty patients were enrolled with 30 patients each allocated to the intervention and control groups. Plasma antibiotic concentrations exceeded the MIC in 82% of patients (18 of 22) in the continuous arm versus 29% (6 of 21) in the intermittent arm ($P = .001$). Clinical cure was higher in the continuous group (70% vs 43%; $P = .037$), but ICU-free days (19.5 vs 17 days; $P = .14$) did not significantly differ between groups. Survival to hospital discharge was 90% in the continuous group versus 80% in the intermittent group ($P = .47$).

Conclusions. Continuous administration of beta-lactam antibiotics achieved higher plasma antibiotic concentrations than intermittent administration with improvement in clinical cure. This study provides a strong rationale for further multicenter trials with sufficient power to identify differences in patient-centered endpoints.

Keywords. pharmacokinetics; clinical outcome; meropenem; piperacillin-tazobactam; ticarcillin-clavulanate.

Severe sepsis is a major cause of mortality worldwide. In Australia and New Zealand, 11.8% of intensive care unit (ICU) admissions are associated with severe sepsis (over 17 000 episodes per annum) with in-hospital mortality of 37.5% and a mortality burden 4 times the Australian annual road toll [1, 2]. This burden is evident globally [3–5]. Early administration of antibiotics active against the infecting organism is a cornerstone of effective management [6]. In a recent point prevalence study of ICU antibiotic usage in Australia and New Zealand, 3 of the 4 most commonly used antibiotics in treatment were beta-lactams, with ticarcillin-clavulanate, meropenem, and piperacillin-tazobactam accounting for 56% of all

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antibiotics used [7]. Given that subtherapeutic dosing is associated with poorer clinical outcomes and increased incidence of drug resistance [8–10], optimal dosing of beta-lactam antibiotics has the potential to improve the outcome for critically ill patients with severe sepsis.

Beta-lactam antibiotics are administered almost exclusively by intermittent bolus dosing [7]. However, there are strong pharmacodynamic data suggesting that this mode of administration may be less effective than administration by continuous infusion. Bacterial killing for beta-lactam antibiotics is related to the duration of time that bacteria are exposed to a concentration of antibiotic that exceeds the minimum inhibitory concentration (MIC), that is, $T_{>MIC}$ [11]. Administration of beta-lactam antibiotics by infusion produces higher blood and interstitial fluid concentrations with greater time above the MIC compared with intermittent dosing, particularly for bacteria with high MIC values, which are common in the ICU [12–14].

Although continuous infusion has been shown to be superior to intermittent administration in animal and ex vivo models, 2 meta-analyses of the human trials to date have not demonstrated differences in clinical cure or survival [11, 15]. These human trials, however, have been primarily conducted in noncritically ill patients and were underpowered, even when pooled, limiting their applicability to patients with severe sepsis. In addition, 13 of the 14 studies included in a recent meta-analysis used nonequivalent dosing in the treatment arms limiting direct comparisons between the 2 delivery methods [11]. The aim of this trial was to determine the clinical and pharmacokinetic differences between continuous and intermittent dosing in critically ill patients with severe sepsis to establish feasibility to proceed with a larger multicenter trial.

METHODS

Study Design and Setting

This prospective, multicenter, double-blind, concealed, randomized controlled trial was conducted at Royal Brisbane and Women's Hospital, Austin Hospital, Blacktown Hospital, and Royal Darwin Hospital, Australia, and Prince of Wales Hospital, Hong Kong. Recruitment occurred between April 2010 and November 2011. Institutional ethics approval for the study was obtained at each site. Consent was obtained from the patient or from a substitute decision maker prior to study enrollment. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000238077).

Selection Criteria

Patients were eligible if they met all of the following inclusion criteria: (1) severe sepsis in the previous 48 hours, defined as confirmed or suspected infection with new organ dysfunction based on diagnostic criteria published elsewhere [1, 16]; (2) planned commencement or commencement within the previous 24 hours of ticarcillin-clavulanate, piperacillin-tazobactam or meropenem; and (3) an expected or actual ICU stay greater than 48 hours. Patients were excluded if they were <18 years of age, had an allergy to one or more of the study medications, were receiving palliative or supportive treatment only, were receiving continuous renal replacement therapy, did not have central venous catheter access with at least 3 lumens (a dedicated lumen was required for study drug administration), or had received the study drug for >24 hours.

Intervention

Patients were randomized to receive either (1) active infusion and placebo boluses (intervention arm) or (2) placebo infusion and active boluses (control arm). The 24-hour dose was clinician-chosen and unaffected by randomization. Ticarcillin-clavulanate and piperacillin-tazobactam (or placebo) infusions were changed every 24 hours, while meropenem (or placebo) infusions were changed 8 hourly, as determined by antibiotic stability at room temperature [17–21]. Labeling was used to conceal the syringe contents for bolus administration. Infusion contents were concealed by dilution of medication in 100–250 mL infusion bags. Both methods of administration were used with the active treatment contained in only one administration route. Clinical staff, data collectors, and patients were blinded to allocation status.

Antibiotic Plasma Levels

A maximum of 3 blood samples per patient were taken immediately prior to the active (or placebo) bolus dose during a 48-hour window period on days 3 and 4 to determine plasma trough levels. Blood samples were centrifuged at 3000 rpm for 10 minutes and the plasma stored at −80°C until batched analysis at a central laboratory; samples were stored at −20°C for <30 hours at one site until storage at −80°C. Antibiotic concentration was determined by validated high performance liquid chromatography [22], which included within-batch calibrators and quality controls [23]. Samples were prepared by protein precipitation with a dichloromethane wash, and the extracts separated on a C18 stationary phase and monitored by ultraviolet. Accuracy and precision of the assays were validated at high, medium, and low concentrations of the calibration range. All results met the bioanalysis acceptance criteria of the US Food and Drug Administration [23]. Free (unbound) drug concentrations were determined using published protein binding values (2% for meropenem, 21% for piperacillin, and 45% for ticarcillin) [24–26].

Outcomes and Measurements

The primary pharmacokinetic endpoint was plasma antibiotic concentration above MIC, scored as a dichotomous variable.

MIC breakpoints for *Pseudomonas aeruginosa* (16 mg/L for piperacillin and ticarcillin, and 2 mg/L for meropenem) were used and scored as positive if all measured free plasma antibiotic concentrations exceeded the breakpoint [27].

Secondary endpoints included clinical response rated by blinded clinicians at a test of cure date 7–14 days after study drug cessation (Table 1) [28]. Time to clinical resolution was defined as the number of days from randomization to the first identified date of clinical resolution; this was set at 28 days for patients who did not achieve clinical cure within a 28-day period. Vital status at ICU and hospital discharge and ICU-free days at day 28 were also evaluated. "ICU-free days" was defined as the number of days alive and free of ICU admission in the first 28 days postrandomization. Daily sequential organ failure assessment (SOFA) scores were recorded [29]. The focus of infection, concomitant antibiotic use, and duration of therapy were recorded. Adverse events during treatment were evaluated as, almost certainly, probably, possibly, or unlikely caused by study medications.

Sample Size

A sample of 60 patients was calculated to achieve a power of 80% to detect a 15% absolute difference in the primary outcome at a significance level of 5%, with a target of 8–16 participants per site.

Randomization and Masking

Randomization was stratified by institution with 1:1 allocation to treatment arm. Following study enrollment, an unblinded research nurse or pharmacist responsible for preparation of the blinded medications determined allocation status by opening a sequentially numbered sealed envelope.

Table 1. Clinician-Rated Outcome Definitions

Clinical response
1. Resolution—disappearance of all signs and symptoms related to the infection 2. Improvement—a marked or moderate reduction in the severity and/or number of signs and symptoms of infection 3. Failure—insufficient lessening of the signs and symptoms of infection to qualify as improvement, including death or indeterminate (no evaluation possible, for any reason)
Clinical cure
1. Resolution—as above 2. All other findings (ie, sum of 2 and 3 above)
Clinical cure (treatment exclusions)
Participants where the study drug, excluding beta-lactam antibiotic de-escalation, was changed due to nonresolution of infection are defined as nonresolution (regardless of clinical response at test of cure date)—otherwise as above

Adequacy of blinding was assessed by clinician survey. A nurse on day 1 or 2 and a medical officer at a later date during study enrollment were asked whether they thought the patient was receiving continuous or intermittent treatment and the degree of certainty in this decision using a 5-point scale [30].

Statistical Analysis

An on-treatment analysis of all patients with plasma antibiotic samples taken on days 3 and 4 was performed for the primary pharmacokinetic endpoint ($n = 22$ and 21 for the intervention and control group, respectively). Free plasma antibiotic concentration differences were analyzed by Mann-Whitney U test and expressed as box (median and interquartile range [IQR]) and whiskers (10–90 percentile). An intention-to-treat analysis of all randomized patients was performed for clinical endpoints ($n = 30$ in each group). The primary outcome was evaluated by Fisher exact test. Secondary outcomes were analyzed by Student t test or Mann-Whitney U test depending on whether inspection of a normal Q-Q plot confirmed or rejected the normality assumption, respectively. A Kaplan-Meier curve, with follow-up until hospital discharge, was plotted to show survival trend; a log-rank test was used to compare treatment groups. Mean ± standard deviation are reported for normally distributed variables and median [IQR] for nonnormal variables. A 2-sided P value <.05 was considered statistically significant. Statistical analysis was conducted using IBM SPSS Statistics 19 (IBM Corporation, Armonk, New York). James and Bang blinding indices [31] were computed using Stata software (StataCorp LP, College Station, Texas). Box and whisker plots were generated in GraphPad Prism 5 (GraphPad Software, Inc, La Jolla, California).

RESULTS

Recruitment and Baseline Characteristics

Sixty patients were enrolled; 16 at Royal Brisbane and Women's Hospital, 14 at Austin Hospital, 12 at Blacktown Hospital, 10 at Royal Darwin Hospital, and 8 at Prince of Wales Hospital. Forty-four patients (73%) completed 4 or more days of randomized treatment, with equal distribution between treatment arms (Figure 1). Four patients were discharged from the ICU within 48 hours of randomization, and 2 patients died during this period. The 24-hour antibiotic dose for the intervention and control groups was comparable: 13.5 [13.5–13.5] g versus 13.5 [11.3–13.5] g for piperacillin-tazobactam, 3.0 [3.0–3.8] g versus 3.0 [3.0–3.0] g for meropenem, and 12.4–13.5 g (2 participants) versus 12.4 g (1 participant) for ticarcillin-clavulanate.

Fourteen patients in each group had a beta-lactam susceptible organism identified as the primary causative organism (Table 2). Four patients in the intervention group had a nonsusceptible organism identified (*Enterococcus* species in 3

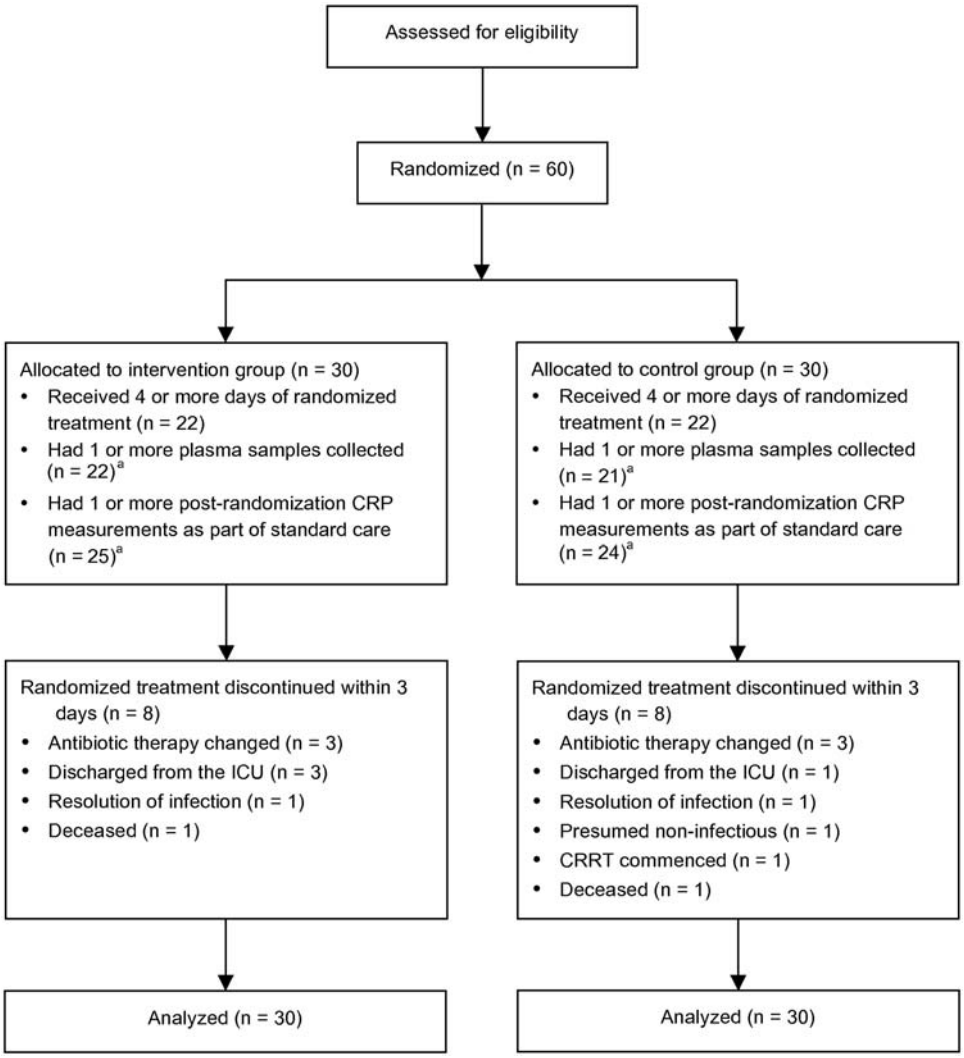

Figure 1. CONSORT flow diagram. Abbreviations: CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVC, central venous catheter; ICU, intensive care unit. [a]Sub-group analysis.

patients and human metapneumovirus in a fourth). Four patients in the control group had a nonsusceptible organism identified: methicillin-resistant *Staphylococcus aureus* in 2 patients, *Coxiella burnetii* (Q fever) in one, and *Stenotrophomonas maltophilia* in a fourth. Baseline characteristics of the 2 groups are reported in Table 3.

Study Endpoints

Plasma antibiotic concentration measured in the first sample was significantly higher in the intervention group compared with the control group for meropenem (9.2 [7.9–12.9] μg/mL vs 3.3 [0.8–4.2] μg/mL), but not for piperacillin (35.6 [21.4–52.0] μg/mL vs 36.4 [6.2–142.2] μg/mL) or ticarcillin (9.1 μg/mL and 130.9 μg/mL vs 14.1 μg/mL, respectively; Figure 2). The ratio of plasma antibiotic concentration to MIC for the intervention and control group is displayed in Figure 3 for all 3 samples: 3.3 [1.9–4.8] μg/mL vs 1.7 [0.4–3.8] μg/mL for sample 1, 3.0 [1.6–4.1] μg/mL vs 1.1 [0.5–6.8] μg/mL for sample 2, and 2.8 [1.5–4.8] μg/mL vs 1.0 [0.3–2.2] μg/mL for sample 3, respectively.

Study endpoints are displayed in Table 4, and survival analysis is shown in Figure 4. For patients receiving meropenem, plasma antibiotic concentration was greater than MIC for all samples in 8 of 8 patients (100%) in the intervention group, compared with 2 of 9 (22%) in the control group; for patients receiving piperacillin-tazobactam, group differences in plasma antibiotic concentration above MIC were 9 of 12 (75%) vs 4 of 11 (36%), and for ticarcillin-clavulanate 1 of 2 (50%) vs 0 of 1, respectively.

Table 2. Organisms Identified on Blood Culture

Organism	Intervention Group	Control Group
MSSA	3[b]	2
MRSA	0	2[c]
Enterococcus spp[a]	3[d,e]	0
Escherichia coli	1	2
ESBL *E. coli*	1	0
Pseudomonas aeruginosa	2[b]	1
Serratia marascens	0	2[c]
Proteus mirabilis	2[e]	0
ABC	1	0
Aeromonas hydrophilia	1[d]	0
Burkholderia cepacia	0	1
Enterobacter cloacae	0	1
Haemophilus influenzae	0	1
Klebsiella oxytoca	1[b]	0
Morganella morganii	0	1
Salmonella typhimurium	1	0
Stenotrophomonas maltophilia	0	1
Streptococcus milleri	1[e]	0
Streptococcus pneumonia	0	1
Streptococcus pyogenes	0	1
Vibrio vulnificus	0	1

Abbreviations: ABC, *Acinetobacter baumanii-calcoaceticus* complex; ESBL, extended-spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

[a] *Enterococcus faecalis* in 2 cases and *Enterococcus* spp (unidentified) in 1 case.

[b–e] Indicate multiple organisms identified in 4 cases.

Table 3. Baseline and Study Characteristics

Characteristic	Intervention Group	Control Group
Sex (male)	23 (76.7%)	19 (63.3%)
Age	54 ± 19	60 ± 19
APACHE II score	21 ± 8.6	23 ± 7.6
Chronic health evaluation		
Respiratory	7 (23.3%)	2 (6.7%)
Cardiovascular	1 (3.3%)	2 (6.7%)
Liver	1 (3.3%)	1 (3.3%)
Renal	0	0
Immunodeficiency	3 (10.0%)	1 (3.3%)
Nil	20 (66.7%)	24 (80.0)
Pre-ICU-acquired infection	25 (83.3%)	21 (70.0%)
Study drug		
Piperacillin-tazobactam	18 (60.0%)	17 (56.7%)
Meropenem	10 (33.3%)	12 (40.0%)
Ticarcillin-clavulanate	2 (6.7%)	1 (3.3%)
Duration of study treatment (days)	5 (2–6.25)	4.5 (2–7)
Organism identified	13 (43.3%)	17 (56.7%)
Site of infection		
Lung	14 (36.8%)	16 (43.2%)
Blood	7 (18.4%)[a]	7 (18.9%)[a]
Intra-abdominal	6 (15.8%)	7 (18.9%)
Skin or skin structure	3 (7.9%)	3 (8.1%)
Urinary tract	3 (7.9%)	2 (5.4%)
Central nervous system	2 (5.3%)[b]	0
Unknown	1 (2.6%)	0
Postrandomization CRP	25 (83.3%)	24 (80.0%)
Plasma samples		
Piperacillin-tazobactam	12 (40.0%)	11 (36.7%)
Meropenem	8 (26.7%)	9 (30.0%)
Ticarcillin-clavulanate	2 (6.7%)	1 (3.3%)
Nil	8 (26.7%)	9 (30.0%)
ICU length of stay (prerandomization)	1 (0–3)	1 (0–4.25)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; ICU, intensive care unit.

[a] Five participants in each group had an additional site of identified infection (lung, urinary tract, and intra-abdominal).

[b] One participant had an additional site of infection (lung).

Adequacy of Blinding

Nursing and medical staff completed a blinding questionnaire for 56 (93.3%) and 51 study participants (85.0%), respectively. Perceptions of randomization status are displayed in Table 5. Of the 33 respondents (30.8%) who believed they knew which treatment arm the participant was in, 13 made a judgment based on physical characteristics of the infusion bag or syringe, and 9 made the judgment with reference to improvement or nonimprovement in the patients' condition, with various reasons provided for the remaining judgments. Blinding indices are reported in Table 6.

Adverse Events

No adverse events occurred as a result of study participation. Two patients died during study enrolment: one patient deteriorated following consent but prior to commencement of the blinded medication with the cause of death septic shock due to aspiration pneumonitis, and one patient with deteriorating respiratory failure and septic shock died 3 days after ICU admission due to pneumonia. Both events were assessed as unlikely to be related to the study drug or intervention.

DISCUSSION

This is the first multicenter ICU trial to our knowledge comparing the effects of continuous and intermittent administration of beta-lactam antibiotics. Our results showed that continuous infusion of beta-lactam antibiotics achieved significant pharmacokinetic separation in $T_{> MIC}$ and higher rates of clinical cure compared with intermittent administration in critically ill patients with severe sepsis. Our study is the only

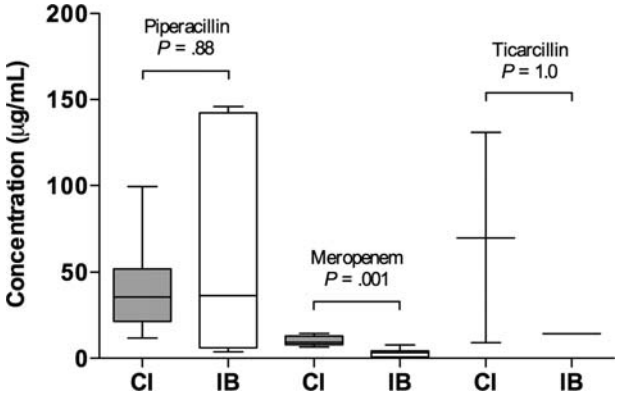

Figure 2. Free plasma antibiotic concentration between treatment groups on the first sample. Abbreviations: CI, continuous infusion; IB, intermittent bolus.

continuous vs intermittent beta-lactam dosing trial that has been conducted in a blinded fashion with allocation concealment [11], and the largest of a limited number of studies conducted exclusively in an ICU setting [28, 32–35]. This multicenter study demonstrated the feasibility of randomizing patients following commencement of 3 commonly prescribed beta-lactam antibiotics for severe sepsis and the ability to administer concealed medications in the ICU in a safe manner.

Continuous infusion has shown to produce higher blood and interstitial fluid concentrations and more rapid bacterial killing, particularly for bacteria with high MIC values in immunodeficient ex vivo and animal models [12–14, 36]. A retrospective study by Lodise and colleagues in critically ill patients with *P. aeruginosa* found that using extended infusions of piperacillin-tazobactam to increase $T_{>MIC}$ resulted in

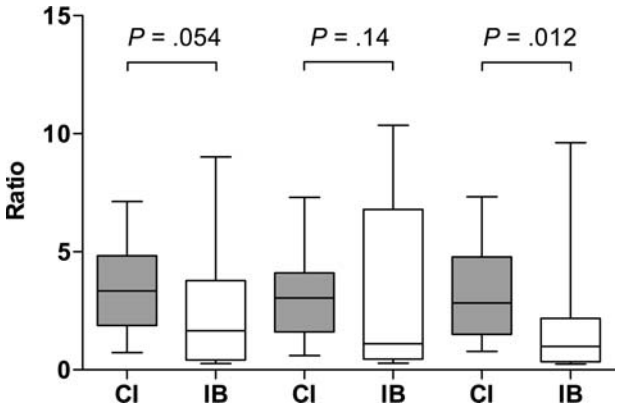

Figure 3. Free plasma antibiotic concentration to minimum inhibitory concentration ratio for 3 samples. Abbreviations: CI, continuous infusion; IB, intermittent bolus.

Table 4. Study Endpoints by Treatment Group

Endpoint	Intervention Group	Control Group	*P*
Plasma antibiotic concentration >MIC	18 (81.8%)[a]	6 (28.6%)[a]	.001
Clinical cure (test of cure date)	23 (76.7%)	15 (50.0%)	.032
Clinical cure (test of cure date with treatment exclusions)	21 (70.0%)	13 (43.3%)	.037
Clinical cure (last day of blinding)	9 (30.0%)	6 (20.0%)	.37
Time to clinical resolution (days)	11 (6.75–24.25)[b]	16.5 (7–28)[b]	.14
Time to resolution of CRP (days)	6 (2.5–22.5)[c]	5 (3–27)[c]	.79
ICU length of stay (postrandomization)	7.5 (4–12)	9 (5–14.25)	.50
ICU-free days			
All	19.5 (12.75–24)	17 (.75–22)	.14
ICU survivors	20.5 (16–24)[d]	18 (12.75–22)[d]	.22
ICU survival	28 (93.3%)	26 (86.7%)	.67
Hospital survival	27 (90.0%)	24 (80.0%)	.47

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; MIC, minimum inhibitory concentration.

[a] Plasma samples were available for 22 and 21 patients in the intervention and control groups, respectively (subgroup analysis).

[b] Time to clinical resolution was set at 28 d for 7 and 13 patients in the intervention and control groups, respectively, as clinical resolution did not occur during this period.

[c] Postrandomization CRP levels were available for 25 and 24 patients in the intervention and control groups, respectively (subgroup analysis); time to resolution of CRP was set at 28 d for 6 patients in each group as CRP was not measured below 100 mg/L during this period.

[d] Subgroup analysis (28 and 26 patients in intervention and control groups, respectively).

improved 14-day survival (12.2% vs 31.6%, $P = .04$) in a subpopulation of patients with high levels of sickness severity (APACHE II score >17) compared with a historical cohort [8]. Another retrospective review of 359 patients treated for gram-negative infections across 14 hospitals in the United States found that extended infusion of piperacillin-tazobactam prolonged survival by 2.8 days ($P < .01$) compared with nonextended infusion of beta-lactam antibiotics [37]. However, apart from a single center ICU study by Roberts and colleagues, which observed a 27% higher cure rate with continuous infusion of ceftriaxone ($P = .06$) [28], our study is the only trial to our knowledge to report a significant difference in clinical cure rates for continuous versus intermittent administration of beta-lactam antibiotics. This may in part by be explained by a focus on patients with a higher acuity of illness and dosing that was independent of treatment arm. Given previous data showing that, in critically ill patients in the ICU,

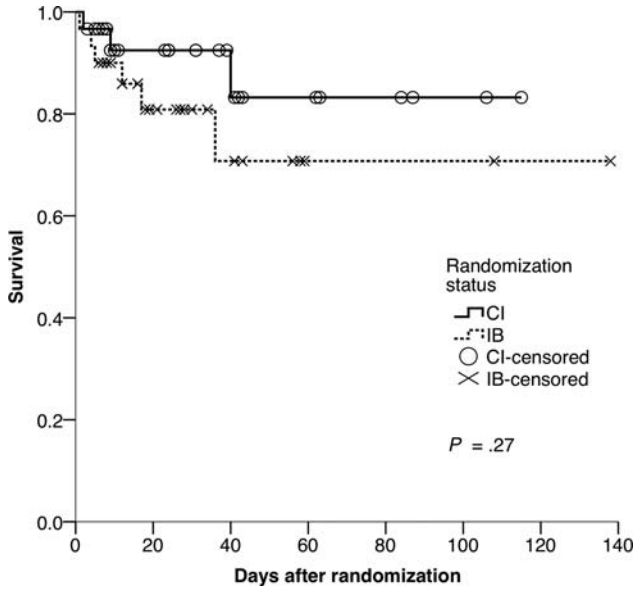

Figure 4. Survival curve for patients in both treatment groups (data have been censored for patients discharged from hospital). Abbreviations: CI, continuous infusion; IB, intermittent bolus.

maintaining 100% $T_{>MIC}$ for beta-lactam antibiotics is associated with greater clinical cure than dosing that results in anything <100% (82% vs 33%, $P = .002$) [9], the nonequivalent dosing between treatment arms (lower in the continuous arm) in 13 of the 14 previous trials may be a significant confounding factor [11]. Our study demonstrated that clinician-determined dosing by continuous infusion might alone be sufficient to improve clinical cure. Although differences in plasma antibiotic concentration between groups were most prominent in patients receiving meropenem, higher rates of 100% $T_{>MIC}$ in measured samples were also present for patients on piperacillin-tazobactam. This was evidenced by the greater concentration range in the piperacillin-tazobactam bolus group, including a greater number of patients with low concentrations.

Table 5. Perception of Blinding Status

Response Category	Nursing Staff		Medical Staff	
	Intervention	Control	Intervention	Control
Strongly believe — continuous	5 (16.7%)	3 (11.5%)	0	0
Somewhat believe — continuous	3 (10.0%)	6 (23.1%)	1 (3.6%)	0
Somewhat believe — intermittent	3 (10.0%)	3 (11.5%)	1 (3.6%	2 (8.7%)
Strongly believe — intermittent	1 (3.3%)	2 (7.7%)	1 (3.6%)	2 (8.7%)
Don't know	18 (60%)	12 (46.2%)	25 (89.3%)	19 (82.6%)

Table 6. Blinding Indices

Measure of Blinding	Nursing Staff Index (95% CI)	Medical Staff Index (95% CI)
James' BI	.76 (.67, .85)[a]	.91 (.84, .97)[a]
Bang's BI — intervention arm	.13 (−.011, .27)[b]	−.036 (−.11, .035)[b]
Bang's BI — control arm	−.096 (−.026, .071)[b]	.13 (.027, .23)

Abbreviations: BI, blinding index; CI, confidence interval.

James' BI reference range (0 to 1): 0 = complete unblinding, .5 = random guessing, 1 = complete blinding. Bang's BI reference range (−1 to 1): −1 = complete blinding, 0 = random guessing, 1 = complete unblinding.

[a] 95% CIs that are >.5 indicate adequate blinding.

[b] 95% CIs that include 0 indicate adequate blinding.

The study was not powered to evaluate any effect on survival and suggests a clinical signal for the surrogate endpoint of clinical cure at 7–14 days after study drug cessation (27% higher in the intervention group), even after adjusting for treatment changes. Additionally, a number of other surrogate clinical endpoints, including ICU-free days at day 28 moved in a favorable direction but did not achieve statistical significance. The progression to achieving a definitive clinical answer via a stepwise research program is well described in the literature [38]. Our study provides an important step in establishing suitable endpoints for a large well-designed prospective phase II multicenter study of continuous administration of beta-lactam antibiotics in critically ill patients with severe sepsis.

The potential benefits to patients and the health system by improved methods of antibiotic delivery of beta-lactam antibiotics are considerable. If a 4% absolute reduction in hospital mortality is achievable (with point estimates of 6.6%–10.0% observed in this study), then this intervention has the potential to save over 800 lives each year in Australia and New Zealand [1], and over 37 000 lives in the United Sates [3]. In addition, in an era of increasingly expensive therapies, administration of beta-lactam antibiotics via continuous infusion compared with intermittent dosing represents greater cost-efficiency in terms of workload and labor costs, while remaining cost neutral in terms of drug costs [14, 36].

This study has a number of limitations. Despite treatment groups being largely well balanced, differences existed for some baseline characteristics, such as 6 years younger mean age, 13% more males, 13% higher comorbidity, and a 13% higher proportion of pre-ICU infections in the intervention group. A modest sample size in each group may have similarly

resulted in potential confounding by unmeasured variables. In terms of plasma antibiotic concentrations, only trough concentrations were measured. Therefore, concentrations at 40%–70% $T_{>MIC}$ could only be inferred to be greater than the MIC. A limited number of extreme concentration values in the intermittent group suggested the presence of some sample timing error.

Clinician blinding is important for surrogate outcomes, such as ICU-free days, which can be influenced by discharge decisions and clinician ratings of clinical cure. Although a minority of staff was able to determine treatment arm by subtle physical indicators, we demonstrated that concealed administration achieved satisfactory levels of blinding in a multicenter context. In particular, compounding of antibiotic medications in infusion bags and labeling of syringes to obscure content for intermittent dosing was sufficient to achieve blinding without the need for more costly and labor-intensive measures, such as colored tubing and covered infusion bags. The finding that medical staff identified the intermittent arm at a significantly higher rate than chance may relate to a smaller sample size, given that a similar identification rate for nursing staff in the intermittent group was nonsignificant.

CONCLUSION

This is the first multicenter ICU trial that we are aware of that compares continuous and intermittent administration of beta-lactam antibiotics. The results provide evidence of the pharmacokinetic separation of continuous infusions against bolus dosing, higher rates of clinical cure associated with continuous infusion, and the feasibility of blinding study medications in a multicenter study. We believe evaluating continuous infusion in a severe sepsis cohort via a phase II randomized controlled trial is both justified and feasible.

Notes

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Potential conflicts of interest. J. A. R. has served as a consultant for AstraZeneca, Pfizer, Gilead and Janssen-Cilag. S. A. R. W. has attended Advisory Boards and acted as a consultant to Janssen-Cilag and AstraZeneca. C. G. has served as a consultant for Janssen-Cilag and Pfizer. J. M. has received travel and speaker fees in relation to investigator-initiated research projects from Fresenius Kabi. D. L. P. has received research grants from AstraZeneca and has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from Three Rivers Pharmaceuticals, Merck, AstraZeneca, SanofiAventis, Pfizer, Johnson & Johnson, and Leo Pharmaceuticals. J. L. has received research grants from AstraZeneca and has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from AstraZeneca, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, and Wyeth Australia. 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.

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Ellie J. C. Goldstein, Section Editor

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].

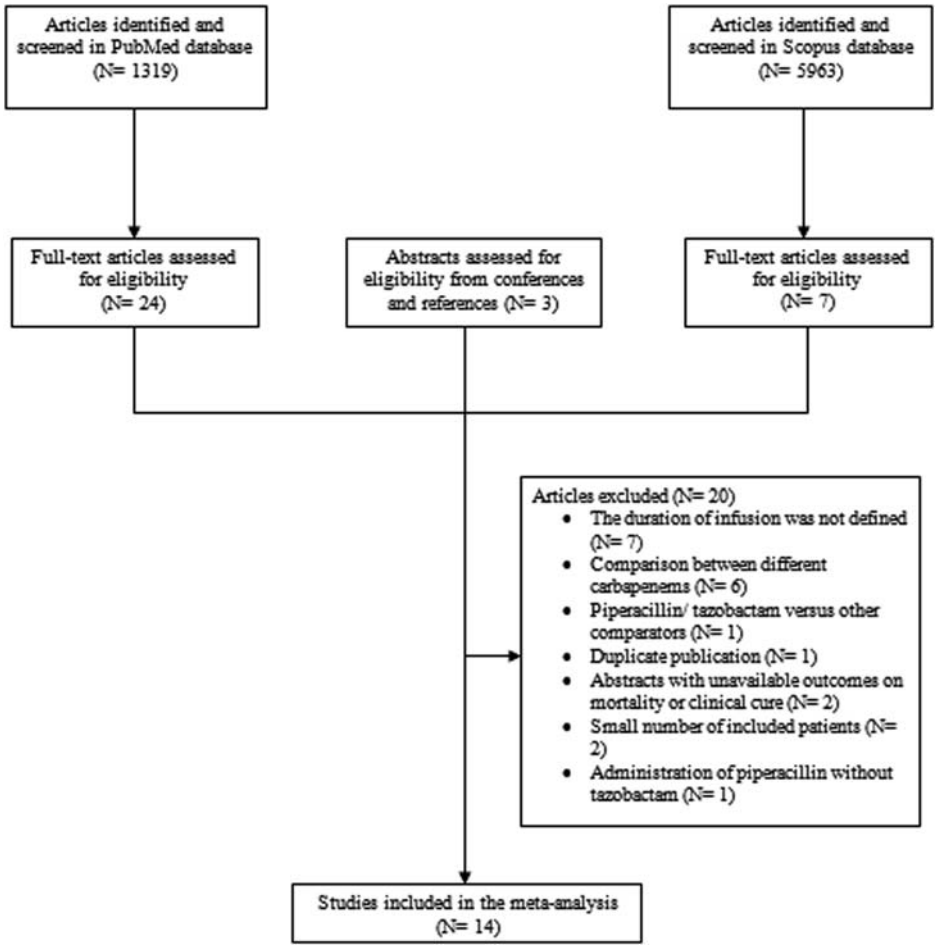

Figure 1. Flow diagram of the selection process of the included studies.

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	*A. baumannii, P. aeruginosa,* 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	*A. baumannii*	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]; *P. aeruginosa* infections	*P. aeruginosa*	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.

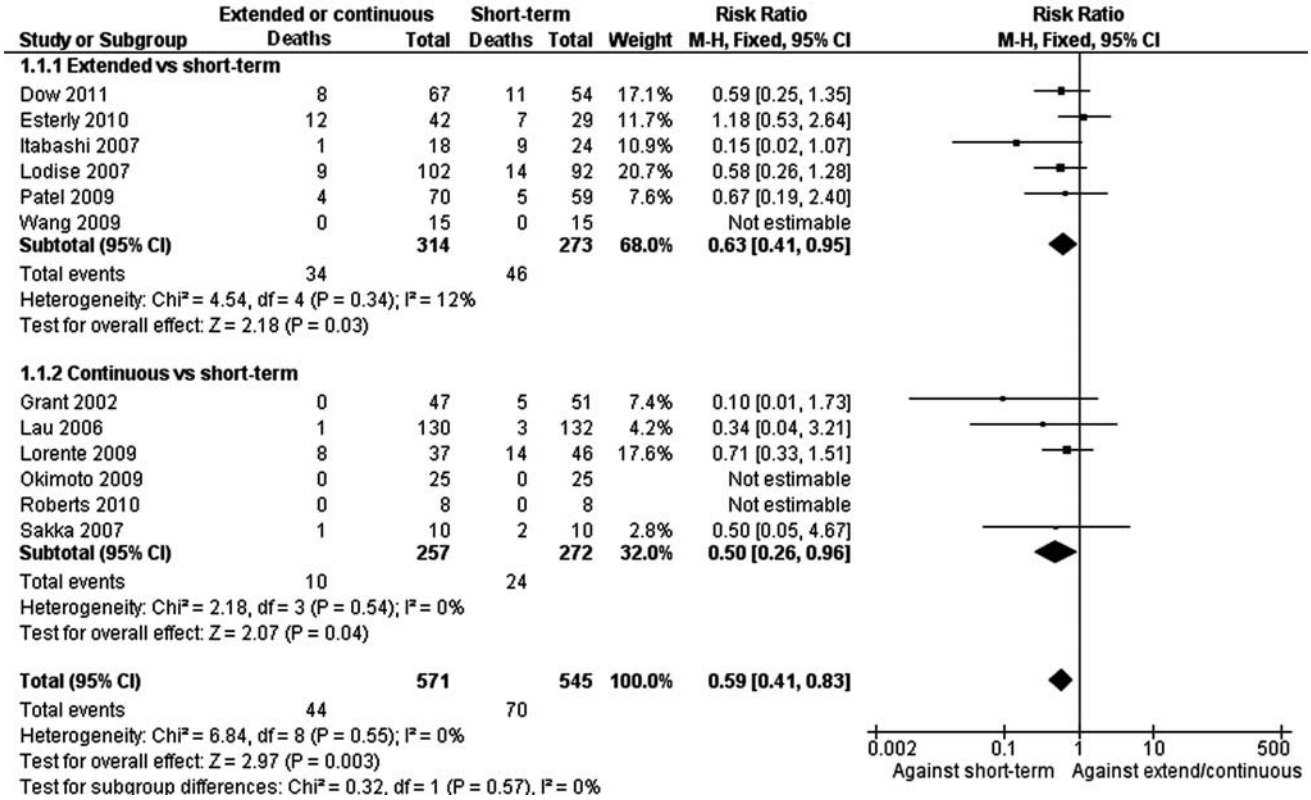

Figure 2. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios; 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/tazbactam 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

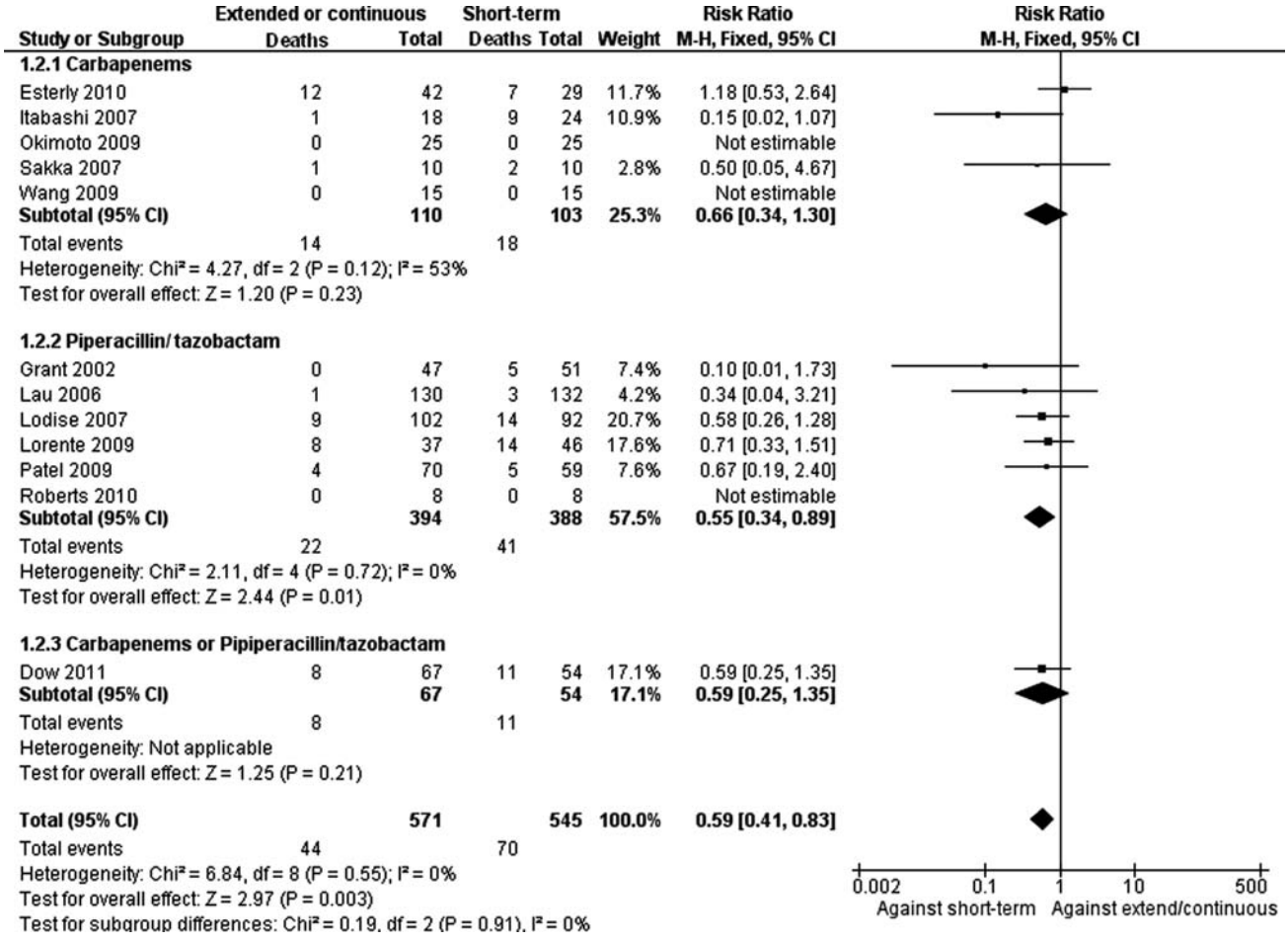

Figure 3. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by the administered antibiotics. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios; 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

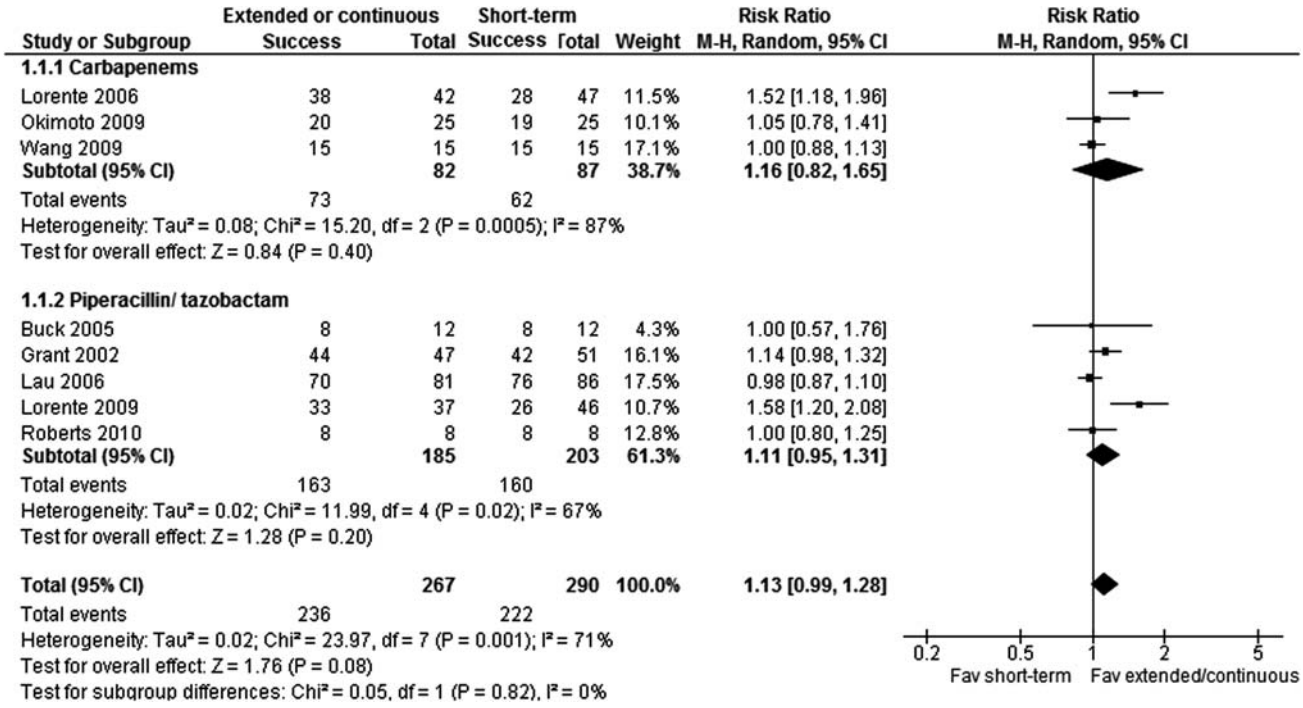

Figure 4. Forest plot depicting the risk ratios of clinical cure of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk 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 pipeperacillin/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.

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