β-lactam prolonged infusion: it's time to implement!

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In the *Lancet Infectious Diseases*, Konstantinos Z Vardakas and colleagues[1] show that prolonged (extended or continuous) infusion of antipseudomonal β-lactams reduced mortality compared with intermittent dosing in a systematic review of randomised controlled trials (RCTs).

Pharmacokinetic and pharmacodynamic measurements are linked to form the pharmacokinetic–pharmacodynamic index that correlates with antibiotic activity. In the case of ß-lactam antibiotics, the index that best correlates with outcomes is the dosing interval in which the free concentration of the antibiotic exceeds the minimum inhibitory concentration (%*f*t>MIC). Currently approved short-term infusion regimens have a more than 80% probability of attaining the pharmacokinetic–pharmacodynamic target across all patient populations and susceptible pathogens.[2] In critically ill patients, both measurements have wide variability and differ from other patient populations. Increased volume of distribution, augmented renal clearance, and hypoalbuminaemia in case of highly protein-bound antibiotics are common causes of pharmacokinetic variability. Infection with less susceptible strains with MICs clustering around the breakpoint, common in intensive care units (ICUs), alter the pharmacodynamics measurement. Rapidly changing physiology, altered renal function, and renal replacement therapy further complicate dosing.[3] Prolonged infusion resulted in higher probability of pharmacokinetic–pharmacodynamic target achievement in ICU settings and critically ill patients seemed to benefit from longer and higher effective antibiotic exposures.[4]

Thus, in vitro studies and pharmacokinetic–pharmacodynamic modelling strongly favour prolonged administration of an optimised dose of β-lactams among critically ill patients, especially with high creatinine clearance and when treating bacteria whose MIC to the administered antibiotic is close to the breakpoint or even higher. Application of a loading dose to reduce the time to achieve therapeutic exposure[5] and therapeutic drug monitoring to adjust the doses[6] also follows biological considerations. However, we need clinical proof for these interventions. We need to see that achieving pharmacokinetic–pharmacodynamic targets translates into clinical benefit overall, considering efficacy and toxicity.

The importance of the current meta-analysis, is that it shows a clear mortality benefit for extended or continuous infusion of β-lactams among critically ill patients. With the exception of two studies contributing only 3·4% of the weight of the meta-analysis for mortality, all studies included in the analysis of mortality were done in ICUs. Although pharmacokinetic–pharmacodynamic considerations are complicated and call for subgrouping of patients by many factors, the meta-analysis simplifies the answer. Overall, for many ß-lactams, different patients and different infections, prolonged infusion of β-lactams in ICU reduced in-hospital mortality. Prolonged infusion is easy to apply in ICU settings. We can foresee no harm with prolonged β-lactam infusion and none has been shown. Surveys have documented variability in clinical practice among physicians, with the large majority of physicians currently using intermittent dosing for β-lactams.[7–9] With current evidence it seems that we should standardise prolonged dosing of β-lactams in ICUs. A loading dose equal to the short-term dose was used in most studies included in the systematic review. When using continuous infusion the dosing regimen should start with a loading dose equal to the short-term dose and continue with the total recommended daily dose administered by prolonged infusion. In case of extended infusion (2–3 h) the recommended doses should be used.

Future RCTs are needed to assess specific questions in and outside the ICU, including the effects and cost-effectiveness of therapeutic drug monitoring. Numerous in-vitro studies indicate that low concentrations of antibiotics promote resistance emergence. The pharmacokinetic–pharmacodynamic indices for resistance suppression might be different or their magnitude higher than the thresholds required for clinical success.[10] Resistance emergence in such RCTs can be assessed by monitoring resistance development in the index isolate, any superinfections and those caused by resistant bacteria, and colonisation with resistant bacteria through standardised surveillance. The discrepancy between clinical failure and the mortality results in Vardakas and colleagues' systematic review clarifies that future RCTs should assess all-cause mortality.

The case of prolonged versus intermittent antibiotic infusion illustrates the importance of systematic reviews and meta-analyses to compile infrequent outcomes. Individual patient data meta-analysis has the capability of addressing the biological complexity of the question through subgroup analysis of individual patient characteristics. In a 2016 individual patient data meta-analysis,[11] only three RCTs were included. Sharing of the databases of completed RCTs would make the most efficient use of research efforts.

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We declare no competing interests.

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Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials

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Summary

Background The findings of randomised controlled trials (RCT), observational studies, and meta-analyses vary regarding the effectiveness of prolonged β-lactam infusion. We aimed to identify the effectiveness of prolonged versus short-term infusion of antipseudomonal β-lactams in patients with sepsis.

Methods We did a systematic review and meta-analysis to compare prolonged versus short-term intravenous infusion of antipseudomonal β-lactams in patients with sepsis. Two authors independently searched PubMed, Scopus, and the Cochrane Library of clinical trials until November, 2016, without date or language restrictions. Any RCT comparing mortality or clinical efficacy of prolonged (continuous or ≥3 h) versus short-term (≤60 min) infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was eligible. Studies were excluded if they were not RCTs, the antibiotics in the two arms were not the same, neither mortality nor clinical efficacy was reported, only pharmacokinetic or pharmacodynamic outcomes were reported, or if ten or fewer patients were enrolled or randomised. Data were extracted in prespecified forms and we then did a meta-analysis using a Mantel-Haenszel random-effects model. The primary outcome was all-cause mortality at any timepoint. This meta-analysis is registered with the PROSPERO database, number CRD42016051678, and is reported according to PRISMA guidelines.

Findings 2196 articles were identified and screened, and 22 studies (1876 patients) were included in the meta-analysis. According to the Grading of Recommendations Assessment, Development, and Evaluation tool, the quality of evidence for mortality was high. Carbapenems, penicillins, and cephalosporins were studied. Patients with variable age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, severity of sepsis and renal function were enrolled. Prolonged infusion was associated with lower all-cause mortality than short-term infusion (risk ratio [RR] 0·70, 95% CI 0·56–0·87). Heterogeneity was not observed (p=0·93, I^2=0%). The funnel plot and the Egger's test (p=0·44) showed no evidence of publication bias.

Interpretation Prolonged infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was associated with significantly lower mortality than short-term infusion. Further studies in specific subgroups of patients according to age, sepsis severity, degree of renal dysfunction, and immunocompetence are warranted.

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Introduction

Despite the availability of multiple antibiotic options, bacterial infections continue to cause substantial morbidity and mortality.[1–3] Changes in both bacterial (mutations, development of resistance) and host factors (older age, immunosuppression, in dwelling devices, operations) created the need for new antibiotics, revival of neglected old antibiotics, and optimised use of the currently available ones.[4–6] Furthermore, in sepsis the volume of distribution (lower albumin levels, increased capillary permeability, and higher extracellular volume) and renal clearance increases resulting in lower antibiotic concentrations.[7]

Most of the new β-lactams display a similar mechanism of action to their predecessors. Therefore, potential optimisation of β-lactams plasma concentrations could improve their clinical effectiveness, which depends on the percentage of time their free plasma concentration is higher than the pathogen's minimum inhibitory concentration (%fT>MIC); the higher this percentage, the higher the effectiveness.[8] Additionally, effectiveness increases when the β-lactam plasma concentration at steady state is more than four times the pathogen's MIC.[8] In patients with normal renal function, the fluctuation of β-lactam plasma concentration improves when prolonged infusion compared with short-term infusion is used.[9]

Preliminary data from small randomised controlled trials (RCTs) and retrospective studies showed that the outcomes depend on the β-lactam class, the quality of the included studies and the infection being studied. Thus, meta-analyses of cephalosporin antibiotics showed no difference in patient outcomes, while improvement in morbidity and mortality was seen in patients treated with carbapenems or piperacillin with tazobactam;[7,10–13] however, subsequent RCTs showed no difference or minor improvements (in terms of clinical cure or improvement but not mortality) in patients treated primarily with continuous meropenem or piperacillin with tazobactam.[14–17] Our primary aim of doing this meta-analysis was to assess the effect of prolonged infusion of

Research in context

Evidence before this study

The plasma concentrations of β-lactams are more stable in patients with, primarily, normal renal function, when prolonged infusions are used compared with short-term infusions. Preliminary data from small randomised contolled trials (RCTs), retrospective studies, and meta-analyses have shown that patient outcomes (primarily mortality) depend on the β-lactam class, the quality of the included studies and the infection being studied. However, subsequent larger RCTs showed no significant difference in mortality with or without improvements in clinical or microbiological cure.

The primary objective of this meta-analysis was the effect of prolonged infusion of antipseudomonal β-lactams (carbapenems, penicillins, cephalosporins, and monobactams) on mortality of patients with sepsis compared with short-term administration (≤60 min). The search in PubMed, Scopus, and Cochrane Library of clinical trials was updated using the same search strategy on April 2017; no additional studies were retrieved. Any RCT studying the comparative clinical efficacy of prolonged (continuous or ≥3 h) versus short-term (≤60 min) infusion of antipseudomonal β-lactams for the treatment of patients with sepsis (community-associated or nosocomial) was considered eligible for inclusion regardless of the primary scope or aim of the trial. We did a meta-analysis using a random effects model.

According to GRADE, the quality of evidence for mortality was high. 17 studies (1597 patients) provided data on mortality at different end-points. Overall, prolonged infusion of antipseudomonal β-lactams was associated with lower all-cause mortality than short-term infusion (risk ratio 0·70, 95% CI 0·56–0·87). Heterogeneity was not observed (p=0.93, I^2=0%). The funnel plot and the Egger's test showed no evidence of publication bias.

Added value of this study

Compared with other similar published works, this meta-analysis is not limited by the inclusion of non-randomised studies, inclusion of RCTs on concentration-dependent antibiotics or on antibiotics with narrower or different antibacterial spectrum, or the presence of inconsistency (heterogeneity was not observed in any of the subgroup or sensitivity analyses). To our knowledge, this meta-analysis of RCTs answering this question has the largest number of included patients from geographically diverse regions. Almost all subgroup and sensitivity analyses showed that prolonged infusion was associated with at least a trend towards lower all-cause mortality than short-term infusion when an adequate number of studies or patients was available.

Implications of all the available evidence

Prolonged infusion of β-lactams might benefit all hospitalised patients with sepsis; however, further studies in specific subgroups of patients according to age, sepsis severity, degree of renal dysfunction, susceptibility of bacteria to the administered antibiotics, and immunocompetence are warranted.

antipseudomonal β-lactams (carbapenems, penicillins, cephalosporins, monobactams) on mortality of patients with sepsis compared with short-term administration (≤60 min).

Methods

Search study and selection criteria

We did a systematic review and meta-analysis to compare prolonged versus short-term intravenous infusion of antipseudomonal β-lactams in patients with sepsis. Two reviewers independently searched PubMed, Scopus, and the Cochrane Library, until November, 2016. We searched PubMed using the following terms without date or language restrictions: ("carbapenem" OR "meropenem" OR "imipenem" OR "doripenem" OR "piperacillin" OR "ticarcillin" OR "cephalosporins" OR "cefepime" OR "ceftazidime" OR "ceftolozane" OR "cefoperazone" OR "monobactam" OR "aztreonam") AND ("extended" OR "prolonged" OR "continuous" OR "discontinuous" OR "intermittent" OR "short" OR "bolus") AND ("duration" OR "infusion" OR "administration" OR "interval" OR "dosing"). We did not search abstracts presented in international conferences. We manually searched the reference lists of selected articles and relevant reviews.

Any RCT studying the comparative effectiveness and safety of prolonged (lasting ≥3 h or 24 h continuous infusion) versus short-term (bolus or up to 60 min intermittent infusion) administration of any anti-pseudomonal β-lactam for the treatment of adult patients with sepsis was considered eligible for inclusion regardless of the primary scope or aim of the trial. Studies evaluating patients with community-acquired, nosocomial, or health-care-associated infections were eligible. Studies were excluded if they were not RCTs, the antibiotics in the two arms were not the same, neither mortality nor clinical efficacy was reported, only pharmacokinetic or pharmacodynamic outcomes were reported, or if ten or fewer patients were enrolled or randomised. Cross-over and cluster RCTs were also ineligible.

Data analysis

Two authors (KZV and GLV) independently extracted data in prespecified forms. Additional data were retrieved by the authors of studies focusing on clinical outcomes via electronic communications. Authors contacted in our previous meta-analysis[10] were not contacted again. The primary outcome was all-cause mortality at any timepoint. When mortality was provided for both the intention-to-treat (ITT) and the per-protocol populations, we used the ITT population. Only if ITT data was not available did we include per-protocol data in the meta-analysis. If mortality

data 30 days from the beginning of treatment were available, this was included in the analysis. If not, any other mortality data was included. Secondary outcomes were clinical efficacy, adverse events, and emergence of resistance.

We used the Cochrane risk of bias tool for methodological assessment. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used for the overall assessment of the evidence in the systematic review.[18] We did the meta-analysis using Review Manager for Windows (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2008). We calculated pooled risk ratios (RR) and 95% CI using the Mantel-Haenszel random-effects model.[19] "Studies were not included in the meta-analysis when there were no events in either arm. RevMan automatically checks for problematic zero counts and adds a fixed value (typically 0·5) to all cells of study results tables when no events occur.[20] Statistical heterogeneity among studies was assessed by χ^2 test ($p<0·10$ indicated significant heterogeneity) and I^2 (degree of heterogeneity). Subgroup analyses were prespecified according to β-lactam class, concomitant antibiotic treatment, bacterial species, renal function, mortality recording time, patients with bacteraemia, primary aim of the study (pharmacokinetic or clinically oriented), age, severity of disease (Acute Physiology and Chronic Health Evaluation [APACHE] II or similar), outcome reporting population (ITT or per-protocol), dose in the two arms (recommended and equal in the two arms, non-recommended but equal in the two arms, and different dose in the two arms), use of a loading dose, and after the exclusion of large studies. We did sensitivity analyses according to the risk of bias. We assessed publication bias by visual inspection of the funnel plot and Egger's test.[21] This meta-analysis is registered with the PROSPERO database, number CRD42016051678, and reported according to PRISMA guidelines.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 2196 retrieved articles, 22 studies (1876 enrolled patients) were included in the meta-analysis (figure 1).[14–17,22–39] Table 1 shows their characteristics. Six studies were designed to study pharmacokinetics and pharmacodynamics of prolonged versus short-term infusion but also provided data for clinical outcomes. Eight evaluated both pharmacokinetics and clinical outcomes and eight studied only clinical outcomes. Most studies were done in Asia-Pacific (ten), followed by Europe (nine), and America (three). Double-blinding was implemented in three RCTs, nine were open-label, and masking was not reported in ten. Allocation concealment was adequate in seven RCTs and in the remaining studies it was inadequate (two) or could not be assessed (13). Generation of random numbers was adequate in four, inadequate in six, and in 12 it was not reported. According to GRADE, the quality of evidence for mortality was high (the true effect lies close to that of the estimate of the effect, appendix p 1).

See Online for appendix

The data (for primary or secondary outcomes) were reported for the ITT population in 14 RCTs, for the per-protocol population in 12 RCTs, and in two RCTs this was not mentioned. The definition of sepsis varied in the individual RCTs: in four it was based on organ dysfunction and in three on systemic inflammatory response syndrome. Known allergies to the study antibiotics, pregnancy, and renal impairment (17 of 20 RCTs reporting exclusion criteria, from renal replacement therapy to creatinine clearance level of 60 mL/min) were the most common exclusion criteria. Septic shock, severe sepsis, impaired liver function, neutropenia, immunocompromise, infections due to strains resistant to study antibiotics, and progressive lethal disease were other less common exclusion criteria. Carbapenems were studied in nine RCTs, penicillins in nine RCTs, and cephalosporins in eight RCTs; monobactams were not evaluated in any RCT.

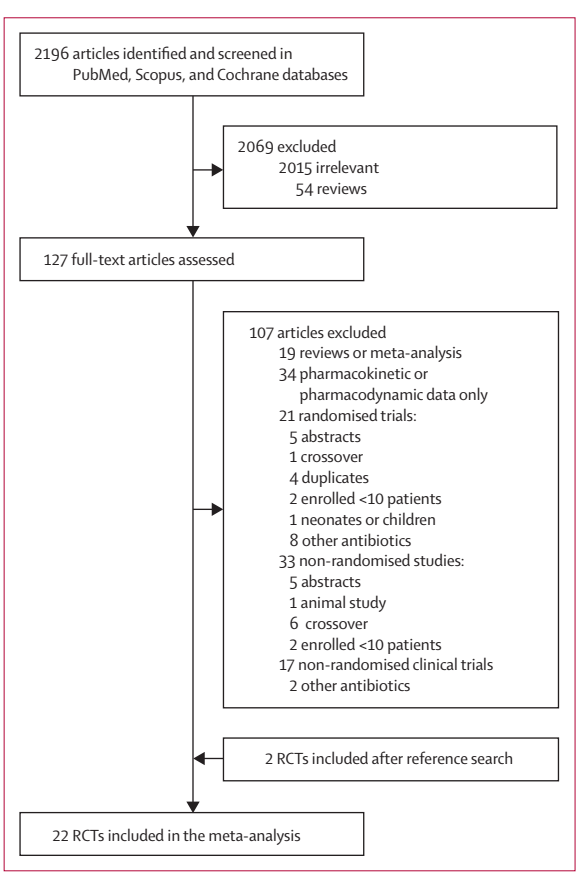

***Figure 1*: Study selection**
RCT=randomised controlled trials.

	Study period; countries; setting	Exclusion criteria	Double blinding	Concealment of allocation	Generation of random numbers	Patients enrolled	Age (mean±SD); APACHE II (mean±SD); CrCl baseline (mean±SD)	Site or type of infection	n/N (%) documented infections	Antibiotic	Treatment prolonged	Treatment short-term	Additional antibiotics allowed; n (%)
Adbul-Aziz (2016)[17]	April, 2013–July, 2014; Malaysia; ICU	Renal replacement therapy, impaired hepatic function, palliative treatment, imminent death	No (open)	Sealed envelope, adequate	Computer blocks, adequate	140	54 (42–63) *vs* 56 (41–68);* 21 (17–26) *vs* 21 (15–26);* 64 (43–98) *vs* 72 (41–122)*	Lung, intra-abdominal, skin and soft tissue, UTI, bacteraemia, CNS	NR	Meropenem, piperacillin/tazobactam, cefepime	Continuous LD;† 3 g/24 h,18 g/24h, 6 g/24 h	30 min; 1 g every 8 h, 4·5 g every 6 h, 2 g every 8 h	Yes; 33 (47%) *vs* 33 (47%)
Bao (2016)[23]	March–October 2012; China; ICU	Shock, CrCl <40 mL/min, pregnancy, resistance to study antibiotics	No (open)	Sealed envelope, adequate	1:1, inadequate	52	69·8 ± 5·9 *vs* 67·0 ± 7·8; 23·2 ± 7·1 *vs* 23·7 ± 6·7 73 (47–251) *vs* 79(53–278)‡	Lung, intra-abdominal infection, UTI, skin and soft tissue	50/50 (100%)	Piperacillin/tazobactam	Extended; 4·5 g every 6 h	30 min; 4·5 g every 6 h	Yes; 3 (12%) *vs* 4 (16%)
Cotrina-Luque (2016)[25]	2011–13; Spain; hospital	Imminent death, mechanical ventilation, CrCl <20 mL/min, septic shock	Yes	List of random numbers, inadequate	1:1, inadequate	78	64·3 ± 14·3 *vs* 63·8 ± 17·3; NR; NR	Lung, intra-abdominal, skin and soft tissue, UTI, bacteraemia, others, unknown	25/78 (32%)	Piperacillin/tazobactam	Continuous LD 2·25 g; 9 g/24 h	30 min; 4·5 g every 8 h	NR
Dulhunty (2015)[16]	2012–14; Australia; New Zealand, Hong Kong; ICU	Palliative or supportive treatment, imminent death	Yes	Sealed envelope, adequate	1:1, inadequate	443	64 (54–72) *vs* 65 (53–72);* 21 (17–26) *vs* 20 (16–25);* NR	Lung, intra-abdominal, skin and soft tissue, UTI, bacteraemia, others, unknown	82/432 (19%)	Meropenem, piperacillin/tazobactam, ticarcillin/clavulanate	Continuous LD; 3 g/24 h, 13·5 g/24 h, 12·4 g/24 h	30 min; 1 g every 8 h, 4·5 g every 8 h, 3·1 g every 6 h	Yes; NR
Lips (2014)[31]	NR; Czech Republic; ICU	Neutropenia, creatinine >280 µmol/L, renal replacement therapy, obesity, pregnancy	No (open)	NR	Block randomisation, adequate	22	63 ± 21 *vs* 57 ± 16; 29 ± 9 *vs* 26 ± 6; 100·9 ± 81·9 *vs* 84·7 ± 49·9	Hospital-acquired pneumonia	NR	Imipenem	3 h extended LD 1 g; 0·5 g every 8 h	30 min; 1 g every 8 h	NR
Wang (2014)[38]	September, 2012–September, 2013; China; ICU	Immunosuppression, neutropenia, pregnancy, concomitant severe infection, renal insufficiency	No (open)	NR	Random number table, adequate	100	63·5 ± 15·3 *vs* 57·2 ± 19·5; 20·7 ± 7·4 *vs* 19·2 ±7·0; NR	Hospital-acquired pneumonia	62/78 (80%)	Meropenem	3 h extended LD 250 mg; 1 g every 8 h	30 min 1 g; every 8 h	Yes; 7 (18%) *vs* 18 (45%)
Dulhunty (2013)[19]	April, 2010–November, 2011; Australia, Hong Kong; ICU	Continuous renal replacement therapy	Yes	Sealed envelope, adequate	1:1, inadequate	60	54 ± 19 *vs* 60 ± 19; 21 ± 8·6 *vs* 23 ± 7·6; NR	Lung, intra-abdominal, skin and soft tissue, UTI, bacteraemia, CNS, unknown	33/60 (55%)	Meropenem, piperacillin/tazobactam, ticarcillin/clavulanate	Continuous, clinician-chosen	Bolus, clinician-chosen	NR
Chytra (2012)[18]	September, 2007–May, 2010; Czech Republic; ICU	GFR <30mL/h, immunodeficiency, immunosuppressant medication, neutropenia	No (open)	Sealed, opaque envelope, adequate	1:1, inadequate	240	44·9 ± 17·8 *vs* 47·2 ± 16·3; 21·4 ± 7·9 *vs* 22·1 ± 8·79; 72 (46–108) *vs* 71 (53–95)*	Lung, intra-abdominal, skin and soft tissue, UTI, bacteraemia, others, unknown	198/240 (83%)	Meropenem	Continuous LD 2 g; 4 g every 24 h	30 min; 2 g every 8 h	Yes; 58 (48%) *vs* 61 (51%)

(Table 1 continues on next page)

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	Study period; countries; setting	Exclusion criteria	Double blinding	Concealment of allocation	Generation of random numbers	Patients enrolled	Age (mean±SD); APACHE II (mean±SD); CrCl baseline (mean±SD)	Site or type of infection	n/N (%) documented infections	Antibiotic	Treatment prolonged	Treatment short-term	Additional antibiotics allowed; n (%)
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Roberts (2010)[35]	NR; Australia; ICU	Renal insufficiency	NR	Opaque sealed envelopes adequate	NR	16	30 (23–40) *vs* 41 (22–65);‡ 20 (16–22) *vs* 24 (18–26);** 97 (327–149) *vs* 89 (53–101)**	Sepsis	NR	Piperacillin/ tazobactam	Continuous LD 4·5 g; 13·5 g/24 h	20 min; 4·5 g every 6 h or every 8 h	NR
Okimoto (2009)[21]	NR; Japan; hospital	NR	NR	NR	NR	50	NR	Community-acquired pneumonia	NR	Meropenem	Continuous 1 g/24 h	NR; 0·5 g every 12 h	NR
Wang (2009)[37]	March, 2006–July, 2006; China; ICU	NR	NR	NR	NR	30	39·7 ± 21·6 *vs* 44·3 ± 21; 17·3 ± 5·8 *vs* 20·3 ± 4·3; NR	Hospital-acquired pneumonia	30/30 (100%)	Meropenem	3 h extended; 500 mg/6 h	60 min;1 g every 8 h	NR
Sakka (2007)[36]	NR; Germany; ICU	Renal replacement therapy	NR	NR	NR	20	62 ± 16 *vs* 59 ± 16; 26 ± 6 *vs* 28 ± 5; 122 ± 33 *vs* 128 ± 35	NR	20/20 (100%)	Imipenem	Continuous LD 1 g; 2 g/24 h	40 min; 1 g every 8 h	NR
Lau (2006)[30]	June, 2002–January, 2014; USA; hospital	Pregnancy, dialysis or CrCl <20 mL/min, neutropenia, immunosuppression, multiorgan failure, irreversible shock	No (open)	NR	1:1, inadequate	262	50·4 ± 16·6 *vs* 49·3 ± 17·8; 8·3 ± 5·8 *vs* 7·6 ± 3·7; NR	Intra-abdominal	174/258 (67%)	Piperacillin/ tazobactam	Continuous LD 2·25 g; 13·5 g/24 h	30 min; 3·375 g every 6 h	NR
Rafati (2006)[34]	October, 2003–March, 2004; Iran; ICU	Dialysis, CrCl <40 mL/min	NR	NR	NR	40	50·1 ± 22·2 *vs* 48·0 ± 20·7; 16·4 ± 6·3 *vs* 14·2 ± 6·1; NR	Lung, intra-abdominal, skin and soft tissue, UTI, bacteraemia	NR	Piperacillin	Continuous LD 2 g; 8 g/24 h	30 min; 3 g every 6 h	Yes; all patients
Buck (2005)	NR; NR; hospital	Late-onset hospital-acquired pneumonia, severe community infections, epilepsy	No (open)	Envelope inadequate	NR	24	60·9 ± 10·3 *vs* 59·8 ± 13; NR; NR	Lung, sepsis, fever of unknown origin, cholangitis	NR	Piperacillin/ tazobactam	Continuous LD 2·5 g; 9 g/24 h	Bolus; 4·5 g every 8 h	NR
Cousson (2005)[26]	NR; France; ICU	CrCl <60 mL/min	NR	NR	Random number table, adequate	16	NR	Ventilator-associated pneumonia	16/16 (100%)	Ceftazidime	Continuous LD 20 mg/kg; 60 mg/kg/24 h	30 min; 20 mg/kg every 8 h	Yes; all patients
Georges (2005)[27]	NR; France; ICU	CrCl <30 mL/min, resistance to study antibiotics, septic shock	No (open)	NR	NR	50	50±17 *vs* 46 ± 24; SAPS II 45 (26–72) *vs* 44; (22–72)**; NR	Hospital-acquired pneumonia, bacteraemia	NR	Cefepime	Continuous 4 g/24 h	30 min; 2 g every 12 h	Yes; all patients
Lubasch (2003)[32]	September, 1998–January, 2000; Germany; hospital	Pregnancy, pneumonia, asthma, cystic fibrosis, immunosupression, progressive lethal disease, CrCl <40 mL/min, shock, mechanical ventilation	No (open)	NR	NR	81	NR	COPD exacerbation	38/81 (47%)	Ceftazidime	7 h extended LD 2 g; 2 g every 12 h	30 min; 2 g every 8 h	NR

(Table 1 continues on next page)

	Study period; countries; setting	Exclusion criteria	Double blinding	Concealment of allocation	Generation of random numbers	Patients enrolled	Age (mean±SD); APACHE II (mean±SD); CrCl baseline (mean±SD)	Site or type of infection	n/N (%) documented infections	Antibiotic	Treatment prolonged	Treatment short-term	Additional antibiotics allowed; n (%)
(Continued from previous page)													
Nicolau (2001)/ McNabb (2001)[33]	NR; USA; ICU	Pregnancy, CrCl <20 mL/min, immunosupression, APACHE II >25, R	No (open)	NR	NR	41	46 ± 16 *vs* 56 ± 20; 13·9 ± 4·4 *vs* 15·5 ± 6·3; 97 ± 32 *vs* 85 ± 33	Hospital-acquired pneumonia	28/35 (80%)	Ceftazidime	Continuous LD 1 g; 3 g/24 h	30 min; 2 g every 8 h	Yes; all patients
Angus (2000)[22]	NR; Thailand; hospital	Pregnancy	NR	NR	NR	34	48 (29–58) *vs* 43 (27–73);‡ 15 (3–23) *vs* 21 (9–27);‡ 38 (5–69) *vs* 23 (8–94)‡	Melioidosis	NR	Ceftazidime	Continuous LD 12 mg/kg; 96 mg/kg per 24 h	Bolus; 40 mg/kg every 8 h	NR
Hanes (2000)[28]	NR; USA; ICU	CrCl <30 mL/min, resistance to study antibiotics	NR	NR	NR	32	33·5 ± 12·5 *vs* 36·1 ± 6; 12·8 ± 4·6 *vs* 10·9 ± 5·8; 96·8 ± 23·3 *vs* 96·8 ± 21·6	Hospital-acquired pneumonia	NR	Ceftazidime	Continuous LD 2 g; 60 mg/kg per 24 h	30 min; 2 g every 8 h	NR
Lagast (1983)[19]	NR; Belgium; hospital	Bilirubin >2 mg/dL, creatinine >2 mg/dL	NR	NR	NR	45	NR	Bacteraemia, UTI, lung, other, unknown	45/45 (100%)	Cefoperazone	Continuous LD 1 g; 4 g/24 h	15 min; 2 g every 12 h	Yes; NR

*Median/mean (IQR) is reported. †Loading dose equal to the short-term dose for meropenem, piperacillin/tazobactam, and cefepime. ‡Median (range) is reported. APACHE=acute physiology and chronic health evaluation. COPD=chronic obstructive pulmonary disease. CrCl=creatinine clearance. ICU=intensive care unit. LD=loading dose. NR=not reported. UTI=urinary tract infection. GFR=glomerular filtration rate.

Table 1: **Study design and baseline patient characteristics of included studies**

The mean or median age of enrolled patients was younger than 45 years in five RCTs (two RCTs in one of the compared groups), 45–65 years in 12 RCTs, older than 65 years in one RCT, and four did not provide relevant data. Most (11) included severely ill patients (mean or median APACHE II ≥20) in at least one of the compared groups (eight RCTs had severely ill patients in both groups), five RCTs enrolled less severely ill patients (APACHE II <20), and in six RCTs the APACHE II score was not reported (Simplified Acute Physiology Score [SAPS] was reported in one RCT). Patients in intensive care units (ICU) only were enrolled in 15 RCTs. When reported, nosocomial lung infections were the most common or the only reason for enrolment. Gram-negative bacteria were the predominant isolates; the frequency of Enterobacteriaceae and non-fermenting Gram-negative bacteria varied between studies. In most of the studies, the cause of sepsis was not documented in a large (up to 81%) proportion of patients. The total daily dose of antibiotics varied both within and between the individual studies (table 1). In 13 of 22 RCTs, patients in the prolonged group received 50–67% of the dose received by those in the short-term group. When reported, the duration of treatment was also variable.

17 studies (1597 patients) provided data for mortality at different endpoints (four reported 30-day mortality, three reported in-hospital mortality, five reported ICU mortality, and 12 RCTs did not specify when death occurred).[14–17,23,24,26–28,30–32,35–39] Overall, prolonged infusion of antipseudomonal β-lactams was associated with lower all-cause mortality than short-term infusion (RR 0·70, 95% CI 0·56–0·87, figure 2). Heterogeneity was not observed (p=0·93, I^2=0%). The funnel plot (appendix p 2) and Egger's test (p=0·44) showed no evidence of publication bias.

Almost all subgroup and sensitivity analyses showed that prolonged infusion was associated with at least a trend towards lower all-cause mortality than short-term infusion (table 2) when an adequate number of studies or patients was available. Analyses that included studies with open labelling, adequate and inadequate generation of random numbers, adequate and inadequate concealment of allocation, continuous infusion, administered antibiotic (figure 3), pharmacokinetics and clinical scope, mean or median age 45 years or older, APACHE II score of more than 20, ITT and per-protocol population analysis, recommended or different dose in the two arms and loading dose showed significant reduction in mortality. Data were not available for subgroup analyses according to specific pathogens or sites of infection, concomitant antibiotic therapy and renal failure or renal replacement therapy (at baseline or during the course of the infection).

Clinical cure or improvement was reported in 18 RCTs (appendix p 3). In both the ITT (11 RCTs, 1219 patients, RR 1·06, 95% CI 0·96–1·17, I^2=39%) and per-protocol (ten RCTs, 1091 patients, 1·13, 1·00–1·28, p=0·06, 57%)

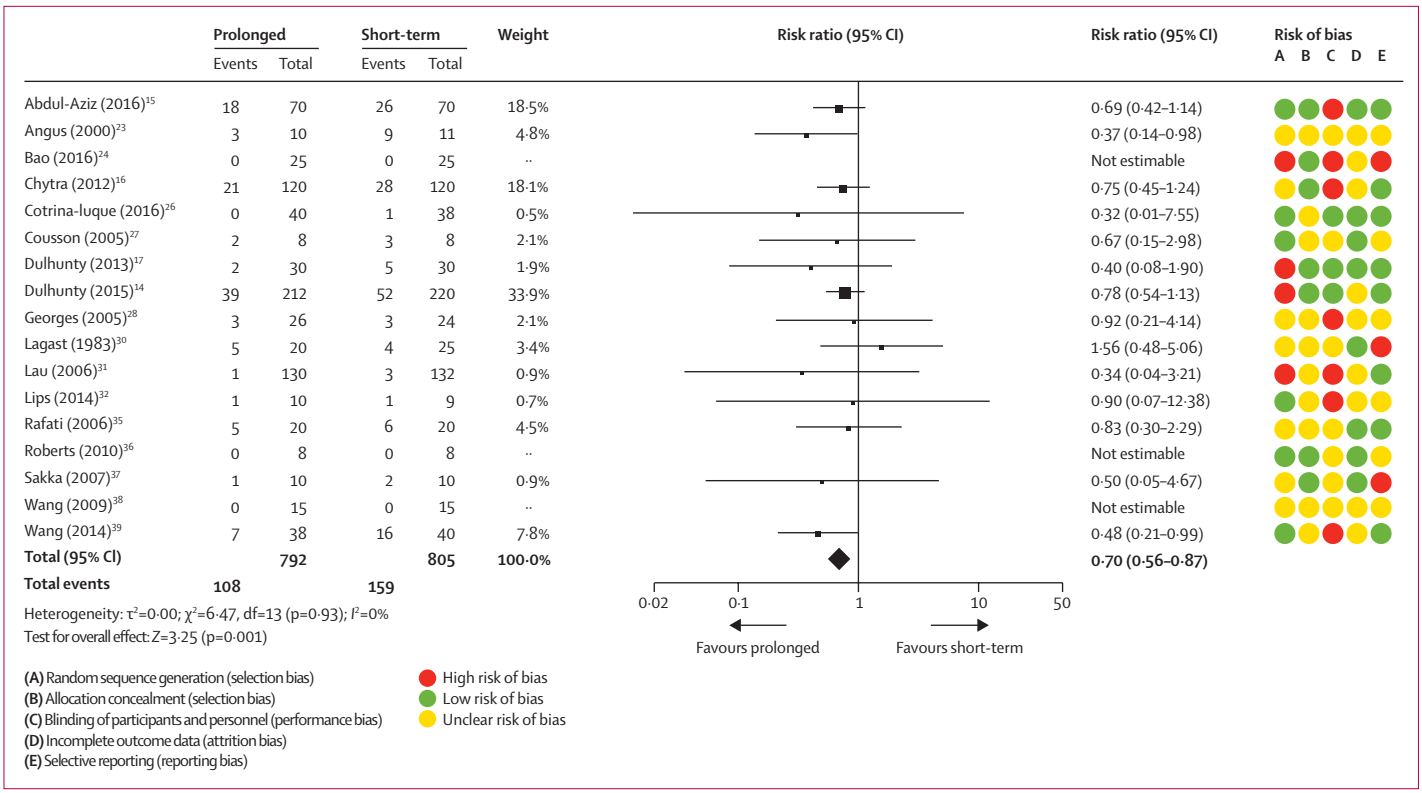

Figure 2: **Forest plot of mortality among patients treated with prolonged versus short-term infusion of antipseudomonal antibiotics**
The areas of squares are proportional to the weight given to each study. Risk ratios are the centres of each square. df=degrees of freedom.

analysis the difference between prolonged and short-term infusion was not significant. Adverse events were not reported in 12 RCTs, were provided for both groups together in two RCTs, and as individual events (for any system but not the patient) in one RCT. There was no difference in reported adverse events between the compared groups (seven RCTs, 980 patients, RR 0·88, 95% CI 0·71–1·09, I^2=0%). Data regarding emergence of resistance were provided by four RCTs. In two of them resistant strains were not isolated in either treatment group. No difference in development of resistance was observed in the other two RCTs (RR 0·60, 95% CI 0·15–2·38).

Discussion

The risk of death in patients with sepsis treated with prolonged infusion of antipseudomonal β-lactams was 30% lower compared with patients treated with short-term infusion. Although some subgroup or sensitivity analyses did not show a significant reduction in mortality, an insufficient number of patients or studies was included in most of these analyses. Clinical cure was not significantly higher with prolonged infusions. We should acknowledge that fewer RCTs provided data on clinical cure than mortality. Furthermore, clinical cure is a more subjective outcome. Data regarding microbiological eradication were also missing, further contributing to the subjective interpretation of clinical cure. The timing of the determination of this outcome varied between studies and this might have also contributed to the lack of statistical significance. Discrepancies between clinical cure and mortality have been reported in other meta-analyses.[40,41] Data regarding adverse events and resistant strains were not studied regularly in the included RCTs.

Compared with other similar published works, this meta-analysis is not limited by the inclusion of non-randomised studies, inclusion of RCTs on concentration-dependent antibiotics or on antibiotics with narrower or different antibacterial spectrum, or inconsistency.[7,10–13,42–47] To our knowledge, this study included the largest number of patients from geographically diverse regions. Additionally, all studied antibiotics are active against a variety of Gram-positive and Gram-negative bacteria, including *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. However, the studied antibiotics are potentially not active against multidrug-resistant Gram-negative and Gram-positive bacteria. Additional studies are required to assess the potential benefit of prolonged β-lactam infusion in such cases.

The difference in effect of the prolonged infusion might have been even higher than the observed due to several factors. Such an example is the higher total dose administered in some of the studies in the short-term group. Additionally, in several RCTs piperacillin with

	Studies	Patients	Risk ratio (95% CI)	Heterogeneity (p value; i^2)
Masking				
Double-blind	3	570	0·74 (0·52–1·06)	0·62; 0%
Open-label	7	839	0·67 (0·49–0·91)	0·89; 0%
NR	7	188	0·70 (0·41–1·21)	0·45; 0%
Generation of random numbers				
Adequate	4	253	0·62 (0·42–0·93)	0·84; 0%
Inadequate	6	1122	0·74 (0·55–0·98)	0·84; 0%
NR	7	222	0·73 (0·42–1·26)	0·44; 0%
Concealment of allocation				
Adequate	7	958	0·73 (0·57–0·94)	0·93; 0%
Inadequate or NR	10	639	0·62 (0·41–0·94)	0·74; 0%
Extended or continuous				
Extended	4	177	0·49 (0·23–1·02)	0·63; 0%
Continuous	14	1433	0·72 (0·58–0·91)	0·92; 0%
Antibiotic class				
Carbapenems	8	574	0·67 (0·49–0·91)	0·93; 0%
Penicillins	8	878	0·70 (0·50–0·98)	0·56; 0%
Cephalosporins	5	145	0·83 (0·40–1·74)	0·23; 28%
Mortality recording time				
In-hospital	3	732	0·78 (0·59–1·03)	0·76; 0%
Intensive care unit	5	891	0·79 (0·59–1·05)	0·96; 0%
Scope of study				
Pharmacokinetics	5	92	0·47 (0·22–0·99)	0·87; 0%
Clinical	7	1165	0·74 (0·56–0·96)	0·57; 0%
Pharmacokinetics or clinical	5	340	0·70 (0·46–1·06)	0·86; 0%
Baseline age				
<45 years	4	307	0·60 (0·31–1·15)	0·20; 38%
≥45 years	11	1229	0·69 (0·54–0·89)	0·97; 0%
NR	2	61	1·13 (0·45–2·85)	0·38; 0%
Baseline APACHE II score				
Both groups ≥20	8	977	0·73 (0·57–0·94)	0·97; 0%
One group ≥20	3	129	0·42 (0·23–0·78)	0·72; 0%
<20	2	302	0·72 (0·28–1·80)	0·47; 0%
NR	4	189	1·00 (0·46–2·14)	0·72; 0%
Analysis population				
ITT	9	1323	0·75 (0·59–0·95)	0·93; 0%
Per-protocol	6	235	0·52 (0·31–0·86)	0·66; 0%
NR	2	36	0·50 (0·05–4·67)	Not applicable
Dose				
Recommended, equal	7	641	0·68 (0·47–0·98)	0·55; 0%
Non-recommended, equal	1	432	0·76 (0·53–1·10)	Not applicable
Different	8	464	0·66 (0·45–0·99)	0·83; 0%
Loading dose in prolonged arm				
Yes	13	1507	0·63 (0·47–0·84)	0·74; 0%
No	4	190	0·56 (0·17–1·85)	0·45; 0%

APACHE II=acute physiology and chronic health evaluation score. ITT=intention-to-treat. NR=not reported.

Table 2: Sensitivity and subgroup analyses for mortality

tazobactam was administered in both arms at a lower daily dose (9–13·5 g) than the recommended by the American Thoracic Society or Infectious Diseases Society of America guidelines and the manufacturer (18 g) for patients with nosocomial pneumonia or neutropenic fever.[14,25,26,35,36,48,49] In this direction, previous studies have shown that in patients with no or mild renal impairment, treatment with 16 g instead of 12 g of continuous infusion of piperacillin was more likely to achieve lung concentrations at least 16 mg/L (piperacillin's breakpoint for Enterobacteriaceae and non-fermenting Gram-negative bacteria).[50] However, although a loading dose has been provided in several RCTs in the prolonged arm, such a strategy was not applied in the short-term arm. The pharmacokinetics of piperacillin with tazobactam are enhanced when it is administered at a dose of piperacillin 8 g with tazobactam 1 g twice daily instead of 4g and 0·5 g four times daily.[51]

Although the prolonged infusion of both carbapenems and penicillins with β-lactamase inhibitors was associated with lower mortality than short-term infusion, prolonged infusion of cephalosporins was not. Another meta-analysis also showed that prolonged administration of cephalosporins did not confer additional benefit to patients compared with short-term infusion.[12] This finding could be attributed to the small number of patients (n=145) and studies (five) or the more heterogeneous population groups (for example patients with melioidosis were also included in this analysis). The current recommended dose for cephalosporins might also be inadequate. For example, the ceftazidime dose (administered as continuous infusion) might need to be increased to 10–12 g/24 h in patients with a glomerular filtration rate higher than 120 mL/min for the treatment of nosocomial pneumonia due to *P aeruginosa* with an MIC of 8 μg/mL.[52]

Several studies allowed for the inclusion of additional antibiotics in the empirical or definitive regimens. The effectiveness of combination regimens is an issue of debate. Meta-analyses have shown that monotherapy is equally effective as combination therapy in patients with variably severe infections.[53–58] However, data favouring combination regimens in cases with multidrug-resistant bacterial infections are emerging.[59,60] Additionally, in cases with infections due to bacteria with MICs at the highest within the susceptible range, in which the probability of death is higher,[61,62] the addition of a second antibiotic could improve patient outcomes through synergy. In one of the included RCTs, mortality with continuous infusion was significantly lower in the subgroup of patients who did not receive additional antibiotics (19% *vs* 43%), but not in those who did (39% *vs* 36%, unpublished data, Mohd H Abdul-Aziz, personal communication).[15]

In cases with infections due to highly susceptible isolates, the contribution of the improved pharmacokinetics of β-lactams with prolonged administration on outcomes might not be significant because the percentage of time that the free plasma concentration of β-lactam is higher than the pathogen's MIC is not expected to be significantly different between prolonged and short-term infusions.[63] Although relevant data were not available for comparisons, clinical cure—but not mortality (unpublished data, Mohd H Abdul-Aziz,

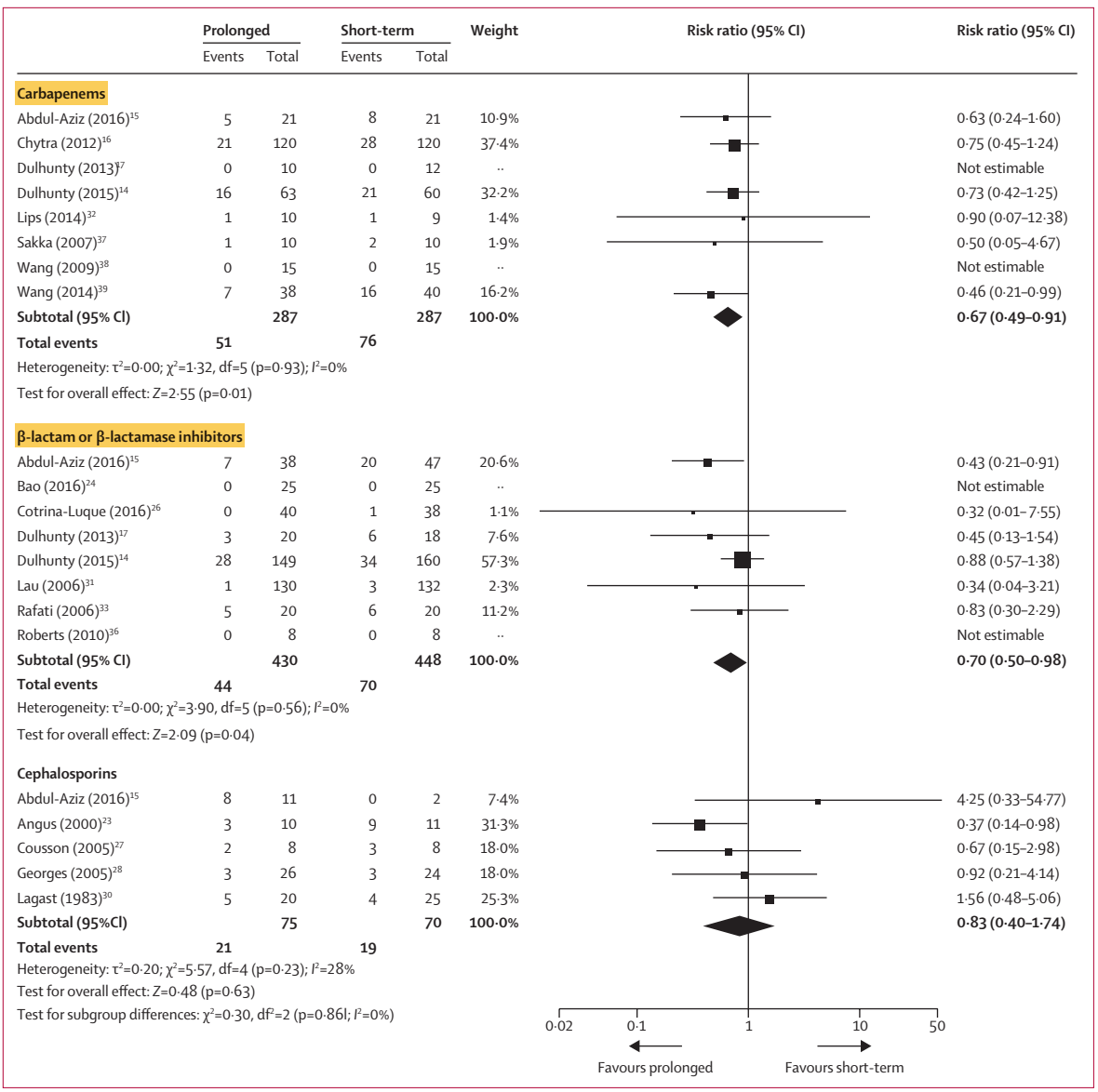

Figure 3: **Forest plot of mortality among patients treated with prolonged versus short-term infusion of antipseudomonal antibiotics according to antibiotic classes**
The areas of squares are proportional to the weight given to each study. Risk ratios are the centers of each square. β-lactam or β-lactamase inhibitors included piperacillin with tazobactam and ticarcillin with clavulanate (in a few cases only). df=degrees of freedom.

personal communication)—was higher in one of the included RCTs in the continuous group when *A baumannii* and *P aeruginosa* were the causative pathogens (52% *vs* 25%, p=0·05), but not when other pathogens were implicated (44% *vs* 38%). Because not only non-fermenting but also several multidrug resistant Gram-negative bacteria usually have higher MICs,[64,65] the effectiveness of prolonged infusion warrants further study in relevant case scenarios.

A significant proportion of studied patients had skin or intra-abdominal infections, whose outcome depends mainly on surgical debridement and not on the appropriate antibiotic regimen. Accordingly, mortality in the RCTs that enrolled mainly patients with surgical infections was generally lower than in RCTs enrolling primarily patients with lung infections.[26] In accordance with previous analyses,[10,66] patients with more severe infections seemed to benefit more from prolonged infusion. In an individual patient data meta-analysis, mortality in the continuous infusion group was marginally lower in patients with APACHE II score of 22 or higher (RR 0·74, 95% CI 0·53–1·01), but not in patients with APACHE II score of less than 22 (RR 0·69, 0·39–1·21). We should acknowledge that the lack of statistical significance could be due to the lack of power.[40]

The outcomes of the meta-analysis cannot be safely extrapolated to patients with variable degrees of renal impairment because this was an exclusion criterion for the majority of RCTs. In patients with renal impairment the difference between prolonged or short-term administration of antipseudomonal β-lactams might not be different when the pharmacodynamics target attainment is for the β-lactam plasma concentration at steady state to be greater than the pathogen's MIC, regardless of the degree of renal impairment (moderate or severe) or renal replacement therapy (with or without remaining renal function).[67–70] However, more favourable exposure might be achieved with prolonged infusions if the pharmacodynamics target is for the β-lactam plasma concentration at steady state to be more than four times the pathogen's MIC. Furthermore, several factors could influence the antibiotic free plasma concentrations that might affect the pharmacodynamics target attainment, including the inter-individual variation, different mode (continuous veno-venous haemofiltration or haemodiafiltration) or intensity (flow rate) in cases of renal replacement therapy or dilution placement (pre-filter or post-filter), residual renal function or progressive renal function restoration, albumin level and antibiotic binding, bacterial MIC, individual antibiotics, and antibiotic dose.[71–75]

In the single published report on patients with renal impairment,[40] there was no difference in mortality between continuous and short-term infusion in the subgroup of patients receiving renal replacement therapy (21 [38%] of 55 *vs* 27 [46%] of 59, RR 0·83, 95% CI 0·54–1·29]. Although the authors stated that "our findings imply that patients receiving renal replacement therapy may not derive a significant benefit from continuous infusion", the power of a hypothetical RCT with such outcomes to detect a 7·6% difference in mortality would be only 13%. Still, no difference in mortality was observed in the analysis of patients not on renal replacement therapy (40 [16%] of 257 *vs* 57 [22%] of 261, 0·71, 0·49–1·03).[40] Additionally, data regarding patients with impaired renal function not on renal replacement therapy were not provided.

Our meta-analysis has certain limitations. First, the outcomes might not apply to older patients (>65 years) because the mean age of enrolled patients was older than 65 years in only one study. However, a proportion of the enrolled patients that could not be quantified were of older age. Second, although there was no evidence of statistical heterogeneity, some clinically meaningful heterogeneity between studies is highly likely (open-label antibiotic use at variable doses, infection severity and type, and patient comorbidity). Third, several small RCTs were included and the probability of small study effects contributing to the favourable outcome for prolonged infusion should be considered. However, analyses that included smaller and larger studies did not show significant discrepancies and similar findings were observed with random and fixed effect models. In this direction, although two RCTs recruiting less than ten patients were excluded, their inclusion was not expected to alter the outcomes since the total number of patients (n=17) and reported events (one) were very small. Fourth, the criteria used in most RCTs for the definition and severity of sepsis are not in accordance to the current definitions.[76]

We did not do analyses regarding microbiologically proven infections (according to individual or groups of bacteria) because these data were absent in the literature. Notably, continuous infusion has been associated with lower mortality in culture-negative (13·4% *vs* 26%, p=0·001) but not culture-positive (33·3% *vs* 26·8%, p=0·3) infections.[40] The clinical significance of this finding warrants further study. Data regarding the specific site of infections also need to be generated. Additionally, duration of masking and in some studies the duration of treatment was relatively short (in five of 13 RCTs the mean or median treatment duration was 5 days or less). Although for both community and nosocomial infections short-duration treatments have been associated with similar outcomes compared with longer ones,[77–80] we are not aware of studies evaluating the effect of such short treatment duration on the outcomes of patients with severe sepsis. Finally, safety assessment was difficult because of under-reporting of adverse events. Although the dose of prolonged infusion in several studies was lower than the dose for short-term infusion, the higher serum concentrations achieved for a longer period of time with prolonged infusion and the higher peak concentrations achieved with short-term infusion could have resulted in more adverse events in either group.

In conclusion, prolonged infusion of antipseudomonal β-lactams in patients with sepsis was associated with lower mortality than short-term infusion; a significant association was evident in several subgroup and sensitivity analyses. The overall quality of evidence was high. The dissociation between the significant reduction in mortality and the non-significant difference in clinical cure requires further investigation. Although the majority of RCTs included only ICU patients, prolonged infusion might benefit all hospitalised patients with sepsis; further studies in specific subgroups of patients according to age, sepsis severity, degree of renal dysfunction and immunocompetence are warranted. The contribution of therapeutic drug monitoring on the outcome of patients treated with prolonged infusion of antipseudomonal β-lactams merits further study.

Contributors
KZV and MEF conceived and designed the study. KZV and GLV did the literature search, extracted the data, and wrote the first draft of the manuscript. KZV and AM analysed the data. KZV, GLV, AM, GS, and MEF contributed to the final draft and revision of the manuscript.

Declarations of interest
We declare no competing interests.

Acknowledgments

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