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Optimal dosing of antibiotics in critically ill patients using continuous/extended infusions: a systematic review and meta-analysis

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Abstract

Introduction

The aim of this study was to determine whether using pharmacodynamic-based dosing of antimicrobials such as extended/continuous infusions in critically ill patients is associated with improved outcomes as compared to traditional dosing methods

Methods

We searched Medline, HealthStar, EMBASE, Cochrane Clinical Trial Registry, and CINAHL from inception to September 2013 without language restrictions for studies comparing the use of extended/continuous infusions to traditional dosing. Two authors independently selected studies, extracted data on methodology and outcomes, and performed quality assessment. Meta-analyses were performed using random-effects models.

Results

Of 1319 citations, 13 randomized controlled trials (RCTs) (n = 782 patients) and 13 cohort studies (n = 2117 patients) met the inclusion criteria. Compared to traditional non-pharmacodynamic-based dosing, RCTs of continuous/extended infusions significantly reduced clinical failure rates (relative risk (RR) 0.68, 95% confidence interval (CI) 0.49 to 0.94, $P = 0.02$) and intensive care unit length of stay (mean difference −1.5, 95% CI −2.8 to −0.2 days, $P = 0.02$), but not mortality (RR 0.87, 95% CI 0.64 to 1.19, $P = 0.38$). There was no significant between-trial heterogeneity for these analyses ($I^2 = 0\%$). Reduced mortality rates almost achieved statistical significance when the results of all included studies (RCTs and cohort studies) were pooled (RR 0.83, 95% CI 0.69 to 1.00, $P = 0.054$).

Conclusions

Pooled results from small RCTs suggest reduced clinical failure rates and intensive care unit length-of-stay when using continuous/extended infusions of antibiotics in critically ill patients. Reduced mortality rates almost achieved statistical significance when the results of RCTs were combined with cohort studies. These results support the conduct of adequately powered RCTs to better define the utility of continuous/extended infusions in the era of antibiotic resistance.

Introduction

Optimal use of antimicrobials is crucial in the critical care setting, especially in an era of rising antibiotic resistance and lack of new antimicrobial development [1]. There is growing interest in alternative antimicrobial dosing strategies that are better aligned with the antimicrobial's pharmacodynamic properties, and the potential of this approach to improve patient outcomes [2]. Given the highly variable and often unknown pharmacokinetics of antimicrobials in critically ill patients as compared to other hospitalized patients, alignment with the pharmacodynamics(PD) of the antimicrobials is even more important [3]. Antimicrobial pharmacodynamics refer to the effects of a drug on microorganisms in relation to the drug's concentration within the body (i.e. pharmacokinetics, PCK). The PD of beta-lactam antimicrobials (e.g. penicillins, cephalosporins, and carbapenems) are termed time-dependent as their effects are best correlated with the amount of time that the serum concentrations of the antimicrobial are above the minimum inhibitory concentration (MIC) of the microorganism. Other antibiotics such as fluoroquinolones and aminoglycosides have PD properties termed concentration-dependent killing given that their effects correlate best with peak concentration/MIC ratio and/or area under the concentration-time curve/MIC ratio [3]. To maximize microorganism eradication, several dosing methodologies that exploit the antimicrobial PD properties have been investigated. These include administration of time-dependent antimicrobials via extended (e.g. over 3–4 hours) or continuous infusion as compared to traditional intermittent infusions (e.g. over 30 minutes), or altering doses based on both patient-specific pharmacokinetic parameters and the MIC of the target organism (also known as dual individualization) [3,4].

Unless clinical benefits are compelling, widespread clinical application of pharmacodynamics based dosing (PDD) is unlikely given the multitude of barriers to their implementation. These barriers include: 1) identification of the types of patients that would benefit the most, with the critically ill patient population being the most obvious choice given their heightened risk of

infectious-related morbidity and mortality and rising resistance, 2) requirement of significant practice changes in microbiology, such as routine MIC determination using more accurate non-automated techniques, 3) better defined pharmacokinetics of antimicrobials in patients in the intensive care unit (ICU) with varying degrees of renal and hepatic dysfunction as well as the extent of medication removal by a variety of renal replacement therapies, and 4) methods to manage the need of a dedicated intravenous line for administration via continuous/extended infusions. To justify such changes, results of rigorously conducted and adequately powered RCTs in a population most likely to benefit (e.g. ICU patients) are needed, the design of which should be informed by comprehensive systematic review of current evidence. Previous systematic reviews that included both critically-ill and non-critically-ill patient populations have provided inconsistent results [5-7]. Therefore to better define the current state of knowledge on this important topic and to update previously reported systematic reviews, we conducted a systematic review and meta-analysis comparing PD antimicrobial dosing to traditional non-PDD on clinical outcomes (mortality, clinical failure rates, and length-of-stay [LOS]) focusing on critically ill patients. We included both randomized and cohort studies but emphasized the results of the RCTs in the interpretation of the results.

Materials and methods

Data sources

With the assistance of a librarian, we systematically searched MEDLINE, HealthStar, EMBASE, Cochrane Clinical Trials Registry, and CINAHL electronically from inception (1948, 1967, 1874, 1966, and 1981, respectively) to September 24, 2013 using the following keywords: critical care, critical illness, intensive care unit, specific names of antibacterial agents, pharmacokinetic, pharmacodynamic, extended infusion, continuous infusion, drug administration, dual individualization. Terms were “exploded” and combined using Boolean operators where appropriate [Additional file 1]. No language restrictions were applied. Reference lists of selected articles and personal files were also searched for relevant citations.

Study selection

Inclusion criteria for this meta-analysis were as follow: 1) adult (> 16 years) critically ill patients, 2) intervention that compared PDD to aid in the determination of antibiotic dosage (i.e. extended infusions, continuous infusions, clinical pathway, and dual individualization principle) to a control group that did not utilize such dosing strategies using either a randomized or non-randomized study design, 3) reporting of any patient outcomes (e.g. mortality, length of stay, clinical failure), 4) any antibacterial whose PD associated with optimal killing is proportion of time during dosing interval that is above the MIC of the pathogenic organism. Studies were excluded if 1) < 50% of patients were admitted to an ICU defined by authors, 2) < 50% adult patients, 3) only Monte Carlo simulation or mathematical modeling data included, 4) no clinical outcomes reported, 5) data published only as an abstract, or 6) different antibiotics were used in the control/intervention groups. Citations were screened in duplicate from the initial results of the search strategy while full text review, also in duplicate, was performed to determine eligibility when either screening reviewer felt a citation potentially met inclusion criteria. Disagreements regarding inclusion were reconciled via consensus.

Data extraction

A standardized data abstraction form was designed prior to the conduct of the literature search. Two reviewers [CC, JF] independently abstracted data from included studies, including data on the publication (i.e. year, author, and country), type of ICU, patient population, study design, interventions used (i.e. antibiotic used, method of dosing), and outcomes (i.e. mortality, ICU and hospital LOS, clinical failure rates). No data on harm (e.g. superinfection, resistance rates) were extracted because very few studies reported such data. Risk of bias in RCTs (including blinding of participants, method of sequence generation and allocation concealment, intention-to-treat analysis, early trial stopping for efficacy before the planned enrollment was completed, and loss to follow up) and cohort studies (including retrospective vs prospective data collection, concurrent vs historical controls, and comparable baseline characteristics of cases and controls) were assessed with disagreements resolved by consensus.

Data analysis

Our primary outcome was all-cause mortality in patients whose infections were managed with PDD (intervention group) as compared to those whose infections were managed by antibiotic dosing that did not incorporate both pharmacodynamic and pharmacokinetic information (control group). Mortality was determined at ICU discharge, hospital discharge, 90, 60, 30 or 28, or 14 days after study enrolment (in descending order of preference). Secondary outcomes were ICU and hospital LOS, and clinical failure as defined by individual study authors (e.g. lack of clinical cure or improvement). Separate analyses were performed using lack of clinical cure alone. Only RCTs were included in the primary analysis and pre-specified subgroup analyses were: 1) by type of study (i.e. RCT and cohort studies), 2) by antibiotic type (e.g. beta-lactam alone, carbapenem alone, cephalosporin alone, piperacillin/tazobactam alone, others), and 3) by intervention (i.e. extended infusions and continuous infusions). All analysis were performed using Review Manager (RevMan version 5.2; Cochrane Collaboration, Oxford, United Kingdom) and random effects models which incorporate between-trial heterogeneity and give wider and more conservative confidence intervals (CI) when heterogeneity is present [8]. We assessed statistical heterogeneity among trials using I^2, defined as the percentage of total variability across studies attributable to heterogeneity rather than chance, and used published guidelines for low (I^2 = 25% to 49%), moderate (I^2 = 50% to 74%) and high ($I^2 \geq$ 75%) heterogeneity [9]. Relative risks (RR) were used to pool binary mortality and clinical failure data and weighted mean differences (MD) to pool continuous LOS data. Ranges [10] and interquartile ranges [11] were converted to standard deviations using previously published methods where necessary. Differences between pooled RR were evaluated using z tests. We considered (two-sided) $p \leq 0.05$ as significant and reported individual trial and summary results with 95% confidence intervals. To assess for publication bias, we visually examined a funnel plot comparing effect measure for the primary outcome of mortality to study precision for evidence of asymmetry.

Results

Study selection

In total 26 studies were included in this meta-analysis [12-37]. The initial search strategy resulted in 1319 citations, of which 69 were retrieved for full review and 21 met all inclusion

criteria and no exclusion criteria [12-28,34-37]. Review of reference lists of the selected studies, other systematic reviews, [5-7] and personal files resulted in 5 additional studies being included [29-33] (Figure 1). The majority of studies were excluded during initial screening because they were Monte Carlo simulation studies that did not involve patients, or were studies that did not involve PDD. The 48 studies were excluded after full review for the following reasons: lack of control group or clinical outcomes [38-64], not discussing pharmacodynamic-based dosing [65-74], Monte Carlo simulations or mathematical modeling [75-81], duplicate publications [82,83], and review articles [84,85].

Figure 1 Flow chart of study selection.

Description of included studies

The characteristics of the studies included in the meta-analysis are described in Table 1. The included studies are international (Europe = 10, USA = 11, Asia = 3, Australia = 2) with a variety of ICU patients (e.g. medical, surgical, trauma, mixed) mainly diagnosed with pneumonia (n = 12). Most studies involved single antibiotic (n = 22), typically with beta-lactam (n = 13) or carbapenem class (n = 6) or both (n = 4). Most employed either continuous (n = 16) or extended (n = 8) infusion interventions, while one was a clinical pathway designed using local antibiogram and MIC information and another using dual individualization principle. Thirteen studies were RCTs, and 13 were cohort studies, of which 4 were prospective and 9 retrospective. All but 2 of the RCTs and all but 2 of the non RCTs were single centre. Sample size ranged from 16 to 240 patients for the RCTs and 32 to 359 for the cohort studies. For the 13 RCTs, only one had the participants blinded to study interventions, while 6 reported allocation concealment and 4 specified that analysis was by intention-to-treat. Only 3 of the RCTs specifically reported that losses to follow up were <5% of randomized patients. For the cohort studies, only 4 of the 13 were prospective and 6 studies employed concurrent control groups. Details regarding assessment of bias amongst individual studies are outlined in Tables 2 and 3.

Table 1 Characteristics of selected studies for meta-analysis

Author (Year) Country	Type of ICU[a]	Study Design	Infection	Illness Acuity		Study Antibiotic	Control Group	Intervention Group
				APACHE II	SAPS II			
Randomized Controlled Trials								
Georges (1999) France [12]	NR	RCT	Pneumonia or bacteremia with gram negative bacilli		47	Cefepime	2 g q12h	4 g/d as CI
Hanes (2000) USA [13]	T	RCT	Nosocomial pneumonia	12		Ceftazidime	2 g q8h (0.5 h infusion)	LD = 2 g (0.5 h infusion), then 60 mg/kg/day as CI
Nicolau (2001) USA [14]	MS, N	RCT	VAP	15		Ceftazidime	2 g q8h (0.5 h infusion)	No LD 3 g over 24 h as CI
Wysocki (2001) France [15]	MS	RCT	Any methicillin-resistant Staphylococcal infections		**	Vancomycin	15 mg/kg q12h (1 h infusion)	LD = 15 mg/kg over 1 h, then 30 mg/kg as CI
Bujik (2002) Netherlands [16]	S	RCT (partial)	Severe intra-abdominal infection	15		Ceftazidime	1.5 g tid (20 min infusion)	LD = 1 g over 20 min, then 4.5 g/d as CI
Georges (2005) France [17]	M, T	RCT	Nosocomial pneumonia or bacteremia		45	Cefepime	2 g q12h (0.5 h infusion)	No LD; 4 g CI
Rafati (2006) Iran [18]	General	RCT	Sepsis from any source	15		Piperacillin alone	3 g q6h (0.5 h infusion)	LD = 2 g over 0.5 h, then 8 g/24 h as CI
Roberts (2007) Australia [19]	General	RCT	Sepsis from any source	18		Ceftriaxone	LD = 500 mg, then 2 g q24h	LD = 500 mg, then 2 g/24 h as CI
Sakka (2007) Germany [20]	NR	RCT	Nosocomial pneumonia	27	44	Imipenem	1 g q8h (40 min infusion)	LD = 1 g over 40 min, then 2 g/24 hr as CI for 3 days, then 1 g q8h over 40 min
Adembri (2008) Italy [21]	M, T	RCT	Sepsis Glycopeptide resistant or failure		45	Linezolid	600 mg q12h (0.5 h infusion)	LD 300 mg, Day 1: 900 mg CI, Day 2 onward: 1200 mg CI
Wang (2009) China [32]	NR	RCT	Acinetobacter pneumonia	19		Meropenem	1 g q8h (1 h infusion)	500 mg q6h as 3 h EI
Chytra (2012) Czech [22]	M	RCT	Severe infection from any source	22		Meropenem	2 g q8h (0.5 h infusion)	LD = 2 g over 0.5 h, then 4 g/d as CI
Dulhunty (2012) Australia [29]	NR	RCT	Severe sepsis	22		Ticarcillin/clavulanate, piperacillin/tazobactam, or meropenem	Dose determined by MD All as intermittent infusion	Dose determined by MD All as CI
Cohort Studies								
Schentag (1984) USA [23]	NR	Cohort	Gram-negative nosocomial pneumonia	NR		Cefmenoxime	Fixed dose 1-2 g q6-8 h	Integration of patient-specific PCK with bacteria-specific killing kinetics (doses ranged from 0.5 g q8h to 2 g q4h)
Lorente (2006) Spain [24]	MS	Cohort	VAP with gram negative bacilli	15		Meropenem	1 g q6h (0.5 h infusion)	LD = 1 g over 0.5 h, then 1 g q6h as CI

Itabashi (2007) Japan [33]	NR	Cohort	Gram- pneumonia	NR	Meropenem	500 mg q12h (0.5-1 h infusion)	500 mg q12 as 4 h EI
Lodise (2007) USA [25]	NR	Cohort	Pseudomonal infections of any source	16	Piperacilin/tazobactam	3.375 g q4 or 6 h	3.375 g q8h as 4 h EI
Lorente (2007) Spain [26]	MS	Cohort	VAP with gram negative bacilli	16	Ceftazidime	2 g q12h (0.5 h infusion)	LD = 1 g over 0.5 h, then 2 g q12h as CI
Lorente (2009) Spain [31]	MS	Cohort	VAP with gram negative bacilli	16	Piperacillin/tazobactam	4.5 g q6h (0.5 h infusion)	LD = 4.5 g over 0.5 h, then 4.5 g q6h as CI
Nicasio (2010) USA [27]	MS, N	Cohort	VAP	19	Cefepime, or meropenem	MD discretion (0.5 h infusions)*	VAP pathway derived by local MICs and PD analysis using Monte Carlo simulations (3 h infusions)
Dow (2011) USA [30]	MS	Cohort	Any infection except CF	25	Piperacillin/tazobactam, or meropenem	P/T 3.375 g q6h or Meropenem 500 mg q6h (0.5 h infusions)	P/T 3.375 g q8h as 4 h EI, Meropenem 500 mg q6h as 3 h EI
Yost (2011) USA [28]	NR	Cohort	Any gram negative infection	~14***	Piperacillin/tazobactam	Variable non-extended infusions of piperacillin/tazobactam, cefepime, ceftazidime, imipenem, meropenem, doripenem	3.375 g q8h as 4 h EI
Akers (2012) USA [34]	Burn	Cohort	Gram positive bacteremia	NR	Vancomycin	1 g q8h (dose adjustment to achieve trough levels 15–20 μg/mL)	3 g as CI (dose adjustment to achieve steady-state levels 20–25 μg/mL)
Lee (2012) USA [35]	NR	Cohort	Gram negative infections	NR****	Piperacillin/tazobactam	2.25-4.5 g q6-8 h (0.5 h infusion)	3.375 g q8h as 4 h EI
Arnold (2013) USA [36]	NR	Cohort	Gram negative infections	20	Cefepime, meropenem, or piperacillin/tazobactam	Cefepime 2 g q8h, meropenem 1 g q8h, piperacillin-tazobactam 4.5 g q6h (0.5 h infusions)q6h (0.5 h infusions)	Same dose/medications as 3 h infusions
Hsaiky (2013) USA [37]	NR	Cohort	Gram negative infections	16	Doripenem	0.5 g q8h (1 h infusion)	0.5 g q8h (4 h infusion)

[a]M = Mixed, MS = Medical Surgical, T = Trauma, C = Coronary, CV = Cardiovascular, N = neurosurgical, NR = not reported.

*Piperacillin/tazobactam used as 24 h infusions in control group and not used in the intervention group.

** only mean SAPS score [86] equal to 14 provided.

*** only midpoint of range provided.

**** median SOFA [87] score of 9.

APACHE II, mean or median acute physiology and chronic health evaluation II score of enrolled patients [88]; CI = Continuous infusion, EI = extended infusion, LD = loading dose, MIC = minimum inhibitory concentration, PD = pharmacodynamic, PCK = pharmacokinetic, RCT = randomized controlled trial, SAPS II, mean or median simplified acute physiology score II score of enrolled patients [89], SOFA, sequential organ failure assessment score [87], VAP = ventilator associated pneumonia.

Table 2 Quality assessment of included randomized controlled trials

Author (Year) Country	# of Centers	# patients	Blinding	Concealed Allocation	Intention to treat Analysis	Stopped early for benefit	Post Randomization Withdrawal
Georges (1999) France [12]	1	18	N	NR	NR	N	NR
Hanes (2000) USA [13]	1	32	N	NR	NR	N	Y (1 from each group)
Nicolau (2001) USA [14]	1	41	N	NR	NR	N	Y (5 from CI group and 1 from control group)
Wysocki (2001) France [15]	10	160	N	Y (consecutive sealed opaque envelopes)	Y	N	Y(15 from CI and 26 from control group)
Bujik (2002) Netherlands [16]*	1	18	N	NR	NR	N	NR
Georges (2005) France [17]	1	50	N	NR	NR	N	NR
Rafati (2006) Iran [18]	1	40	N	NR	NR	N	NR
Roberts (2007) Australia [19]	1	57	N	Y (sequential opaque sealed envelopes)	Y	N	N
Sakka (2007) Germany [20]	1	20	N	Y (sealed envelopes)	NR	N	NR
Adembri (2008) Italy [21]	1	16	N	Y (closed envelopes)	NR	N	Y (1 died, 1 developed ARF; group(s) not specified)
Wang (2009) China [32]	1	30	N	NR	NR	N	NR
Chyta (2012) Czech [22]	1	240	N	Y (sealed opaque envelopes)	Y	N	N for mortality and LoS, but Y (14 in CI and, 12 in control group) for cure data
Dulhunty (2012) Australia [29]	5	60	Y	Y (sequentially numbered sealed envelopes)	Y	N	N

Y = Yes, N = No, NR = Not reported, CI = continuous infusion, LoS = length of stay.

* Partial randomization: first six patients allocated to continuous infusion group, next 12 patients randomized to continuous infusion or intermittent administration groups.

Table 3 Quality assessment of included cohort studies

Author (Year) Country	# of centers	# Patients	Prospective/Retrospective	Concurrent Control	Comparable Baseline
Schentag (1984) USA [23]	1	32	Prospective	N (historical)	NR
Lorente (2006) Spain [24]	1	89	Retrospective	Y (physician discretion)	Y
Itabashi (2007) Japan [33]	1	42	Prospective	Y (physician discretion)	Y
Lodise (2007) USA [25]	1	194	Retrospective	N (historical)	Y
Lorente (2007) Spain [26]	1	121	Retrospective	Y (physician discretion)	Y
Lorente (2009) Spain [31]	1	83	Retrospective	Y (physician discretion)	Y
Nicasio (2010) USA [27]	1 (3 separate ICUs)	168	Prospective	N (historical)	Y (except less intervention patients with liver disease)
Dow (2011) USA [30]	1	121	Retrospective	N (historical)	Y
Yost (2011) USA [28]	14	359	Retrospective	Y (physician discretion)	N, (Higher use of concomitant aminoglycosides, pseudomonas infections, and rates of positive cultures from respiratory and other sources in control patients)
Akers (2012) USA [34]	1	171	Retrospective	Y (physician discretion)	Y (except control group received ~10% lower average dose)
Lee (2012) USA [35]	2	148	Retrospective	N (historical)	Y (except control group more COPD patients, more concomitant use of fluoroquinolones and aminoglycosides, and longer (~1d) duration and higher (~13%) cumulative dose of therapy)
Arnold (2013) USA [36]	1	503	Prospective	N (historical)	Y (except control group more COPD patients, more endotrachial (vs bronchioalveolar lavage) cultures, less *Hemophilus influenza*, and more use of meropenem)
Hsaiky (2013) USA [37]	1	86*	Retrospective	N (historical)	Y (except control group had lower proportion of patients with positive blood cultures)

* Data from 86 critically ill patients of 200 enrolled hospitalized patients reported separately.
COPD, chronic obstructive pulmonary disease.

Morbidity and mortality

The 13 RCTs [12-22,29,32] included data from 782 patients and the 13 cohort studies [23-28,30,31,33-37] from 2117 patients. Two studies [28,37] enrolling all hospitalized patients reported mortality data separately for patients requiring ICU admission. Reduction in mortality (9 RCTs, n = 620, RR 0.87, 95% CI 0.64 to 1.19, p = 0.38) almost achieved statistical significance when the results of all included studies (RCTs and cohort studies) were pooled (19 studies, n = 2354, RR 0.83, 95% CI 0.69 to 1.00, p = 0.054) (Figure 2). Focusing the pooled analysis on only RCTs, PDD significantly reduced clinical failure rates, defined as either lack of clinical cure or improvement (7 RCTs, n = 565, RR 0.68, 95% confidence interval [CI] 0.49 to 0.94, p = 0.02) (Figure 3) and ICU LOS (5 RCTs, n = 442, mean difference −1.5, 95% CI-2.8 to −0.2 days, p = 0.02) (Figure 4). There was no significant between-trial heterogeneity for these analyses (I^2 = 0%). Incorporating pooled data from non RCTs also yielded significantly reduced clinical failure rates but with increased heterogeneity (Figure 3). PDD did not result in reduced hospital lengths of stay, but few studies reported this outcome (Figure 5). Visual inspection of the funnel plot comparing the effect measure (RR) for the primary outcome of mortality for each study with its precision, expressed as the standard error of the natural logarithm of RR, SE(log[RR]) did not suggest asymmetry (Additional file 2).

Figure 2 Effects of pharmacodynamic-based antibiotic dosing on ICU [15-17,22,29]**, hospital** [30,34,36,37]**, 14-day**[25]**, 30-day** [35]**, or unspecified (ICU or hospital)** [18-21,27,28,31,33] **mortality grouped by RCT vs cohort studies.** Individual study RR with 95% CI are shown as squares with lines and pooled RRs with 95% CI, calculated using random-effects models both overall and separately for each subgroup, are shown as diamonds. The interaction p-value, calculated using a Z-test, testing for subgroup differences between the RCT and cohort studies, was not significant (p = 0.61). The pooled results for the RCTs were essentially unchanged if ICU mortality was replaced by the more prolonged hospital mortality for the studies that also provided this data [22,29] (9 RCTs, 620 patients, RR 0.86, 95% CI 0.64 to 1.17, p = 0.34, I^2 = 0%), or if the results of the partial RCT [16] were excluded (8 RCTs, 602 patients, RR 0.88, 95% CI 0.64 to 1.21, p = 0.42, I^2 = 0%). Weight refers to the weighting of each individual study to the overall pooled RR. CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial; RR, relative risk.

Figure 3 Effects of pharmacodynamic-based antibiotic dosing on clinical failure, defined as lack of clinical cure or improvement, grouped by RCT vs cohort studies. Individual study RR with 95% CI are shown as squares with lines and pooled RRs with 95% CI, calculated using random-effects models both overall and separately for each subgroup, are shown as diamonds. Z-tests were used to test for subgroup differences. If clinical failure is defined only as lack of clinical cure, results were identical for the non RCTs and similar for the RCTs (7 RCTs, 525 patients, RR 0.83, 95% CI 0.70 to 0.99, p = 0.04, I^2 = 11%) and overall (14 studies, 1509 patients, RR 0.68, 95% CI 0.52 to 0.88, p = 0.004, I^2 = 70%). Weight refers to the weighting of each individual study to the overall pooled RR. CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial; RR, relative risk.

Figure 4 Effects of pharmacodynamic-based antibiotic dosing on ICU length of stay, grouped by RCT vs cohort studies. Individual study RR with 95% CI are shown as squares with lines and pooled RRs with 95% CI, calculated using random-effects models both overall and separately for each subgroup, are shown as diamonds. Z-tests were used to test for subgroup differences. IQR [22,29,35,36] converted to standard deviations by dividing by 1.35 as previously described [11], or standard deviations calculated from reported 95% confidence intervals assuming equal standard deviations between groups[30]. Weight refers to the weighting of each individual study to the overall pooled RR. CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial; SD, standard deviation.

Figure 5 Effects of pharmacodynamic-based antibiotic dosing on hospital length of stay, grouped by RCT vs cohort studies. Individual study RR with 95% CI are shown as squares with lines and pooled RRs with 95% CI, calculated using random-effects models both overall and separately for each subgroup, are shown as diamonds. Z-tests were used to test for subgroup differences. Ranges [25] or IQR [22,36,37] converted to standard deviations using the methods of Hozo [10] or by dividing by 1.35 as previously described [11], respectively, or standard deviations calculated from reported 95% confidence intervals assuming equal standard deviations between groups [30]. Weight refers to the weighting of each individual study to the overall pooled RR. CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial; SD, standard deviation.

Subgroup analysis

Examining effects by types of antibiotics (Figure 6), only studies involving piperacillin/tazobactam (or piperacillin alone) clearly demonstrated a survival advantage for the intervention group (5 studies [18,25,28,31,35], n = 683, RR = 0.62, 95% CI 0.46-0.85, p = 0.003, I^2 = 0%), although only 1 of 5 studies in this subgroup was an RCT [18]. Studies involving carbapenems almost demonstrated a survival advantage for the intervention group (4 trials [20,22,33,37], n = 388, RR 0.64, 95% CI 0.41 to 1.00, p = 0.051, I^2 = 0%), with 2 of 4 studies being RCTs [20,22]. With respect to type of intervention, extended infusions, all of which were cohort studies, improved survival (8 studies [,25,27,28,30, 33,35-37], n = 1580, RR 0.72, 95% CI 0.54 to 0.96, p = 0.03, I^2 = 42%). Improved survival in the studies using continuous infusions did not achieve statistical significance (9 RCTs [15-22,29] and 2 cohort studies [31,34], n = 874, RR 0.97, 95% CI 0.76 to 1.25, p = 0.84, I^2 = 0%) (Figure 7).

Figure 6 Effects of pharmacodynamic-based antibiotic dosing on mortality separated by class of antibiotic. Individual study RR with 95% CI are shown as squares with lines and pooled RRs with 95% CI, calculated using random-effects models separately for each class of antibiotic, are shown as diamonds. Weight refers to the weighting of each individual study to the overall pooled RR. CI, confidence interval; IV, inverse variance; RR, relative risk.

Figure 7 Effects of pharmacodynamic-based antibiotic dosing on mortality comparing continuous to extended infusion subgroups. The continuous infusion studies included 9 RCTs [15-22,29] and 2 cohort studies [31,34], whereas the extended infusion studies included only cohort studies. Individual study RR with 95% CI are shown as squares with lines and pooled RRs with 95% CI, calculated using random-effects models both overall and separately for each subgroup, are shown as diamonds. The interaction p-value, calculated using a Z-test, testing for subgroup differences between continuous and extended infusion studies, did not achieve statistical significance (p = 0.12). Weight refers to the weighting of

each individual study to the overall pooled RR. CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial; RR, relative risk.

Discussion

Pooled results from small RCTs suggest that PDD, employing primarily continuous or extended infusions of antibiotics, reduces clinical failure rates and ICU LOS in critically ill patients when compared to traditional dosing methods. Reduced mortality rates almost achieved statistical significance when the results of RCTs are combined with cohort studies.

Unlike previous meta-analyses, our systematic review only included data from critically-ill patients, stratified results by RCTs vs. cohort studies, included all clinically used antibacterial agents, and a larger number of studies. We were able to demonstrate a statistically significant improvement in clinical outcomes (reduced clinical failure rates) and ICU LOS even when exclusively methodologically more rigorous RCT data are pooled. Three previous meta-analyses, each with fewer studies, included both critically-ill and non-critically-ill patients and found somewhat different results. Two of these meta-analyses found either no benefit [5,6] or that clinical outcomes were improved only when the same dose of antibiotic was given as continuous infusions when compared to intermittent infusions [6]. Our more comprehensive and updated search included all of the RCTs in ICU found in previous systematic reviews plus additional studies, which may have contributed to these differences. Similar to the most recent meta-analysis [7], we also found that mortality improvement was seen with continuous/extended infusions of only piperacillin/tazobactam and carbapenems in ICU patients, largely due to data from non-RCTs.

Our pooled results, at least from RCTs, were consistent between studies. This lack of statistical heterogeneity occurred despite significant differences between studies in types of antibiotics used, interventions studied (i.e. extended or continuous infusions, or other pharmacodynamic-based dosing strategies), dosages of antibiotic used (i.e. whether both arms of the study received the same dose of antibiotic, whether loading doses were given), types of organisms or infections studied, and whether concomitant pharmacokinetic data (i.e. therapeutic drug monitoring) was also performed to validate the dosing strategies. Indeed we found piperacillin/tazobactam as the most studied antibiotic, and the only one that resulted in a clear improvement in mortality, albeit largely due to cohort studies. In our study, extended infusions but not continuous infusions demonstrated a statistically-significant reduction in mortality. This is inconsistent with the theoretical background, given that extended infusions may not result in serum antibiotic concentrations that are above the minimum inhibitory concentration (MIC) of the infecting pathogen throughout the entire dosing interval, and our findings may be due to methodological differences given that all of the extended infusion studies were non-randomized while all but two of the continuous infusion studies were RCTs. However, while for antibiotics such as beta-lactams and carbapenems the commonly accepted PD parameter associated with improved cure rates are free drug concentration above MIC for 40-70% of the dosing interval, these parameters have not been subjected to rigorous clinical evaluation in multiple studies, and their validity have been recently challenged [90]. In addition, it is well known that pharmacokinetic parameters are highly variable in critically ill patients due to a variety of factors [91], and thus whether any PD targets were actually attained by any interventions should ideally be confirmed using actual pharmacokinetic measurements in each individual study to better correlate with clinical and other endpoints. For example, augmented renal clearance, seen in some critically ill septic and trauma patients

[92] might lead to an inability to achieve concentrations above the MIC due to greater clearance in some patients, and this would have a greater impact on continuous vs extended infusions.

As evident from the list of studies included in this meta-analysis, PDD strategies are not a new concept. Indeed, the concept of dual-individualization incorporating both patient PCK and bacterial PD information to arrive at dosage regimen dates back to the 1980s [23]. Even the concept of extended or continuous infusions would benefit from individualization using patient-specific PCK parameters and organism-specific MIC in order to verify that these infusions did indeed reach the PD target. Given the intense resources required for such an intervention (i.e. infrequently reported PCK of antibiotics in ICU patients, or bacteria-specific MIC for each infection), this concept has not been universally adopted. More recently, given the rise in bacterial resistance and dearth of new antibiotics, significant attention has been paid to optimizing use of currently existing antibiotics through, for example, extended/continuous infusions. Practically speaking, it is still not an accepted standard of practice for all institutions to report MIC for all organisms despite having these MICs determined by automated systems due to errors associated with automated techniques, and there are still a large number of unknowns when it comes to PCK parameters in ICU patients. Therefore to truly translate the knowledge from the plethora of *in vitro* / Monte Carlo type studies to actual ICU patients, significant system changes and further research as previously outlined needs to occur. This systematic review of primarily small, single-centre studies of critically-ill patients, a patient population that is most likely to benefit due to their severity of illness and increased potential for infections with more resistant organisms, suggests that PDD may lead to improved patient-centered clinical outcomes and supports the conduct of more adequately powered and rigorously performed RCTs to confirm these findings.

The strengths of our study include the use of rigorous systematic review and meta-analytic methods consistent with PRISMA guidelines [93] including a reproducible and comprehensive literature search strategy without language restrictions, clearly defined inclusion criteria, duplicate citation review, data abstraction, and quality assessment of individual studies, and a pre-defined statistical analysis plan. Our meta-analysis also included more studies of critically ill patients: previous meta-analyses included only 5–7 studies enrolling primarily critically ill patients of which only 2–6 were RCTs [5-7], whereas our meta-analysis included 26 studies enrolling primarily critically ill patients of which 13 were RCTs.

Our study also has limitations. The numbers of patients enrolled in the selected studies were relatively small, and most of the RCTs were unblinded and single centre, with only a minority reporting on quality indicators such as allocation concealment, intention-to-treat analysis, and losses to follow up post randomization. This makes further subgroup analysis not useful given the small sample size in each study and the types of studies. To be comprehensive, we included all antibacterials, all study types, and all dosages of antibiotics and also studies targeting different PD endpoints which resulted in clinical heterogeneity among included studies. Surprisingly, the pooled results, at least among RCTs, demonstrated no statistical heterogeneity; however, tests for heterogeneity have lower statistical power when the number of trials is small. Clinical cure is a subjective outcome that was defined by each study's authors, and potentially subject to bias given that the studies were mainly unblinded [94], and the microbiological causes of infections were different, and appropriateness of empiric antibiotics, a key determinant of outcomes, were not reported. Even a moderately sized additional RCT could negate the statistical significant improvement

in this outcome. For example, a recently completed blinded placebo-controlled RCT in critically ill patients with ventilator associated pneumonia [95], which did not meet our inclusion criteria because it compared two different antibiotics for different durations of therapy (extended [4 h] dose doripenem for 7 days vs intermittent dose imipenem/cilastin for 10 days), found higher clinical failure rates in the extended dose doripenem group (43/79 [54%] vs 38/88 [43%]). Adding data from this trial to our pooled result would make the improved clinical failure rates among the continuous/extended RCTs no longer statistically significant: 8 RCTs, n = 732, RR 0.81, 95% CI 0.57 to 1.15, p = 0.24. It would also eliminate statistically significant mortality improvements in the subgroup of extended infusion cohort studies, and the subgroup of carbapenem studies. In addition, almost all studies included in this review permitted the use of concomitant antibiotics [12,14-19,21,22,24-31,34-37], whereas the remainder did not specifically report on whether their use was permitted [13,20,23,32,33]. This use of concomitant antibiotics may have contributed to reduced differences in outcomes between groups. We also did not conduct our analysis controlling for differences in antibacterial dosing regimes (e.g. with or without loading doses) or patient severity of illness. The latter would require patient-level data which would be challenging to acquire.

Conclusions

In conclusion, pooled results from small RCTs suggests that PDD reduces clinical failure rates and ICU LOS in critically ill patients, and may reduce mortality rates when the results of RCTs are combined with cohort studies. Given the limitations of our review, these findings support the conduct of future adequately powered and well designed RCTs to confirm these findings for this important clinical question.

Key messages

- Pooled analysis of randomized controlled trials suggest that continuous/extended infusions of antibiotics in critically ill patients improves cure rates, length of stay, and possibly mortality.
- This study adds to the current body of literature by focusing on critically ill patients and including a larger number of studies without restriction on type of antibiotics.

Abbreviations

CI, Confidence interval; ICU, Intensive care medicine; LOS, Length-of-stay; MIC, Minimum inhibitory concentration; PCK, Pharmacokinetic; PD, Pharmacodynamic; PDD, Pharmacodynamic based dosing; RCT, Randomized controlled trial; RR, Relative risk

Competing interests

On behalf of all authors, the corresponding author states that there is no competing interest.

Authors' contributions

CC contributed to the design of the study, data collection, data analysis, and wrote the initial draft of the manuscript and revised subsequent drafts. AL contributed to data collection and analysis, and contributed to the draft of manuscripts. JF contributed to the design of the study, data collection and analysis, and also to the revisions of the manuscripts. All authors have approved the final draft of the manuscript.

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Additional files

Additional_file_1 as PDF

Additional file 1 Search Strategy. Description: Detailed search strategy used to identify relevant citations in the MEDLINE database. Similar search strategies were used for the other databases.

Additional_file_2 as PDF

Additional file 2 Funnel Plot. Description: Funnel plot comparing the effect measure, relative risk (RR), for the primary outcome of mortality for each study, including both randomized controlled trials and cohort studies, with its precision, expressed as the standard error of the natural logarithm of RR, SE(log[RR]).

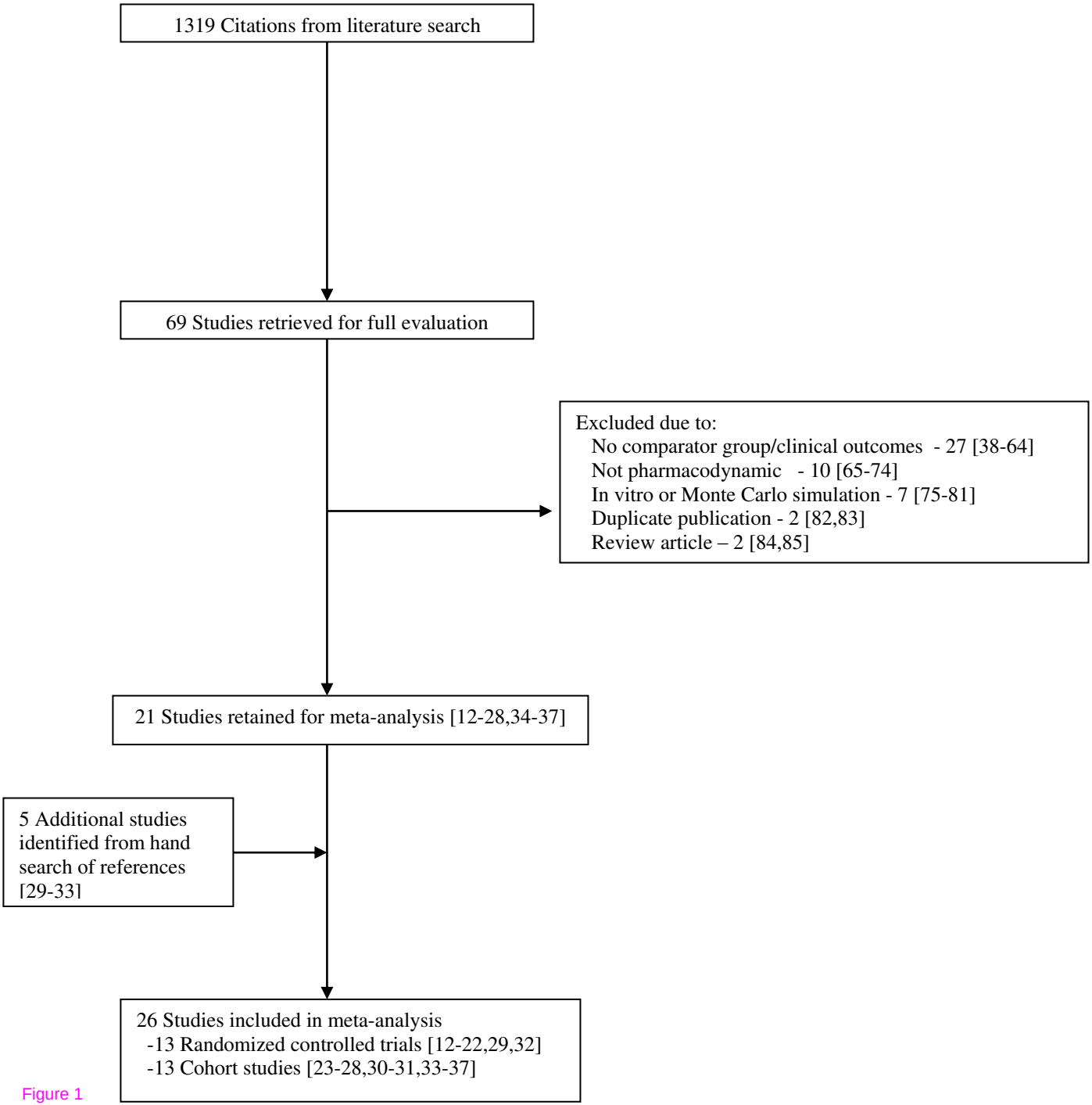
1319 Citations from literature search
69 Studies retrieved for full evaluation
Excluded due to:
No comparator group/clinical outcomes - 27 [38-64]
Not pharmacodynamic - 10 [65-74]
In vitro or Monte Carlo simulation - 7 [75-81]
Duplicate publication - 2 [82,83]
Review article – 2 [84,85]
21 Studies retained for meta-analysis [12-28,34-37]
5 Additional studies identified from hand search of references [29-33]
26 Studies included in meta-analysis
-13 Randomized controlled trials [12-22,29,32]
-13 Cohort studies [23-28,30-31,33-37]

Figure 1

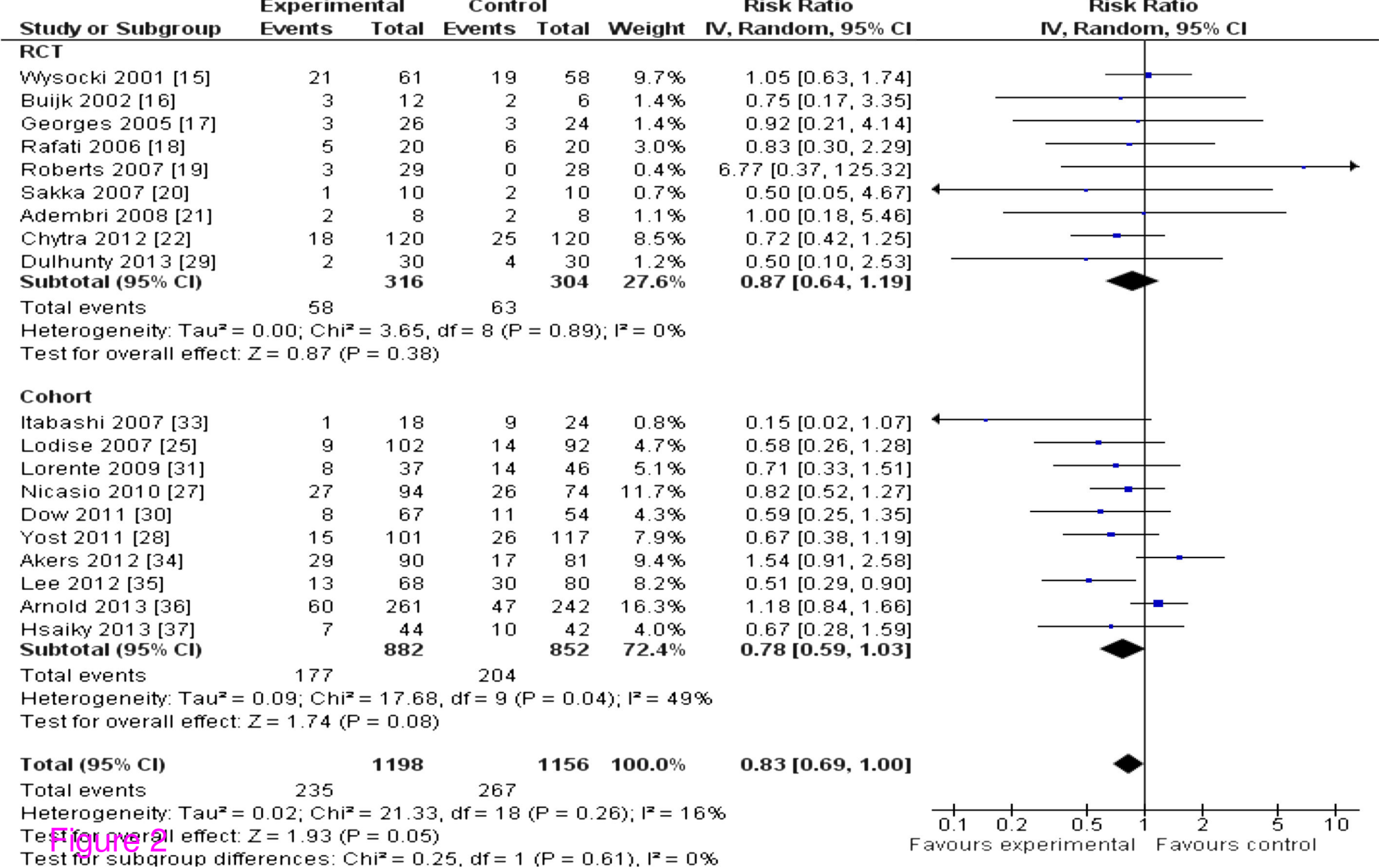
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
RCT
Wysocki 2001 [15] 21 61 19 58 9.7% 1.05 [0.63, 1.74]
Buijk 2002 [16] 3 12 2 6 1.4% 0.75 [0.17, 3.35]
Georges 2005 [17] 3 26 3 24 1.4% 0.92 [0.21, 4.14]
Rafati 2006 [18] 5 20 6 20 3.0% 0.83 [0.30, 2.29]
Roberts 2007 [19] 3 29 0 28 0.4% 6.77 [0.37, 125.32]
Sakka 2007 [20] 1 10 2 10 0.7% 0.50 [0.05, 4.67]
Adembri 2008 [21] 2 8 2 8 1.1% 1.00 [0.18, 5.46]
Chytra 2012 [22] 18 120 25 120 8.5% 0.72 [0.42, 1.25]
Dulhunty 2013 [29] 2 30 4 30 1.2% 0.50 [0.10, 2.53]
Subtotal (95% CI) 316 304 27.6% 0.87 [0.64, 1.19]
Total events 58 63
Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 8 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)
Cohort
Itabashi 2007 [33] 1 18 9 24 0.8% 0.15 [0.02, 1.07]
Lodise 2007 [25] 9 102 14 92 4.7% 0.58 [0.26, 1.28]
Lorente 2009 [31] 8 37 14 46 5.1% 0.71 [0.33, 1.51]
Nicasio 2010 [27] 27 94 26 74 11.7% 0.82 [0.52, 1.27]
Dow 2011 [30] 8 67 11 54 4.3% 0.59 [0.25, 1.35]
Yost 2011 [28] 15 101 26 117 7.9% 0.67 [0.38, 1.19]
Akers 2012 [34] 29 90 17 81 9.4% 1.54 [0.91, 2.58]
Lee 2012 [35] 13 68 30 80 8.2% 0.51 [0.29, 0.90]
Arnold 2013 [36] 60 261 47 242 16.3% 1.18 [0.84, 1.66]
Hsaiky 2013 [37] 7 44 10 42 4.0% 0.67 [0.28, 1.59]
Subtotal (95% CI) 882 852 72.4% 0.78 [0.59, 1.03]
Total events 177 204
Heterogeneity: Tau² = 0.09; Chi² = 17.68, df = 9 (P = 0.04); I² = 49%
Test for overall effect: Z = 1.74 (P = 0.08)
Total (95% CI) 1198 1156 100.0% 0.83 [0.69, 1.00]
Total events 235 267
Heterogeneity: Tau² = 0.02; Chi² = 21.33, df = 18 (P = 0.26); I² = 16%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.61), I² = 0%
0.1
0.2
0.5
1
2
5
10
Favours experimental
Favours control

Figure 2

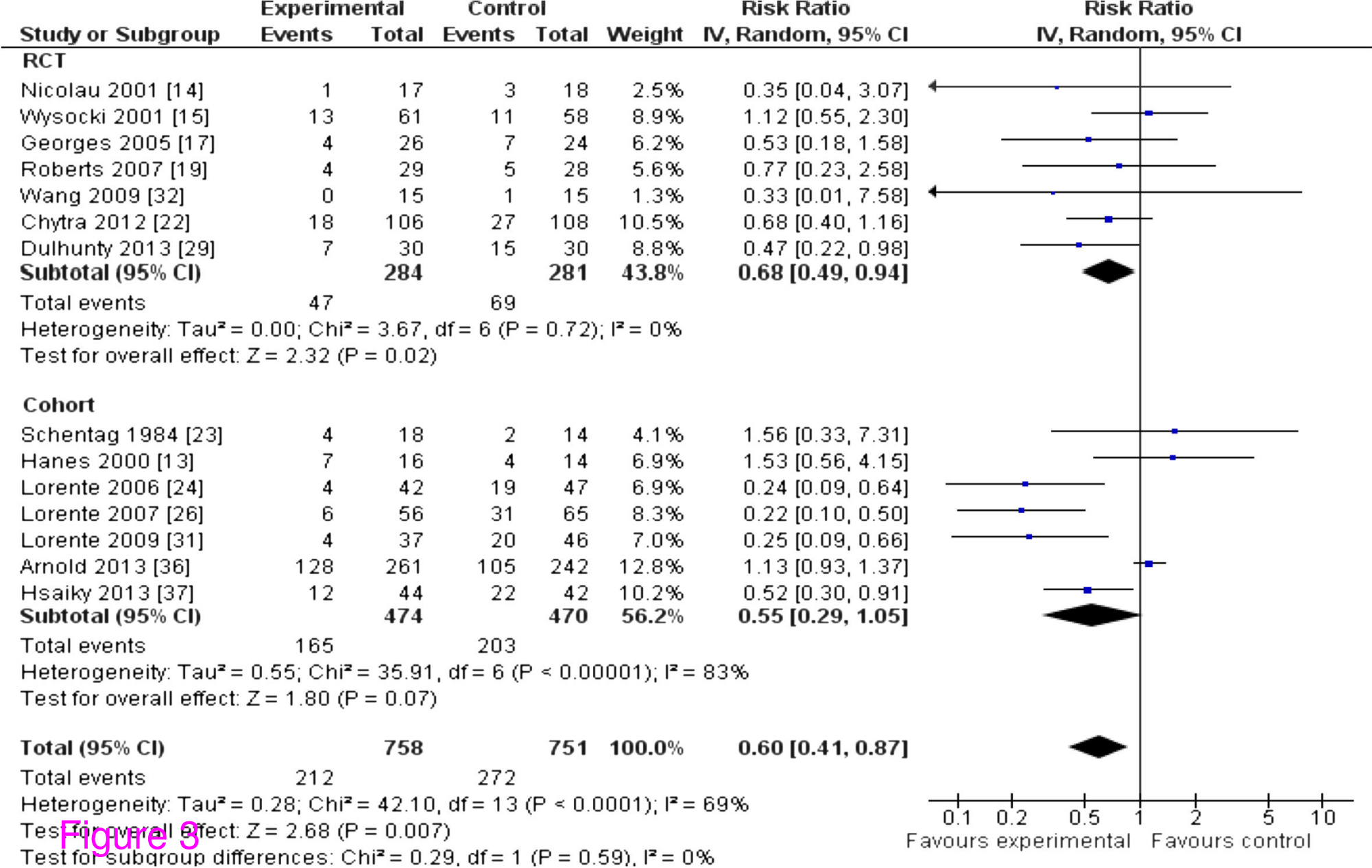
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
RCT
Nicolau 2001 [14] 1 17 3 18 2.5% 0.35 [0.04, 3.07]
Wysocki 2001 [15] 13 61 11 58 8.9% 1.12 [0.55, 2.30]
Georges 2005 [17] 4 26 7 24 6.2% 0.53 [0.18, 1.58]
Roberts 2007 [19] 4 29 5 28 5.6% 0.77 [0.23, 2.58]
Wang 2009 [32] 0 15 1 15 1.3% 0.33 [0.01, 7.58]
Chytra 2012 [22] 18 106 27 108 10.5% 0.68 [0.40, 1.16]
Dulhunty 2013 [29] 7 30 15 30 8.8% 0.47 [0.22, 0.98]
Subtotal (95% CI) 284 281 43.8% 0.68 [0.49, 0.94]
Total events 47 69
Heterogeneity: Tau² = 0.00; Chi² = 3.67, df = 6 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)
Cohort
Schentag 1984 [23] 4 18 2 14 4.1% 1.56 [0.33, 7.31]
Hanes 2000 [13] 7 16 4 14 6.9% 1.53 [0.56, 4.15]
Lorente 2006 [24] 4 42 19 47 6.9% 0.24 [0.09, 0.64]
Lorente 2007 [26] 6 56 31 65 8.3% 0.22 [0.10, 0.50]
Lorente 2009 [31] 4 37 20 46 7.0% 0.25 [0.09, 0.66]
Arnold 2013 [36] 128 261 105 242 12.8% 1.13 [0.93, 1.37]
Hsaiky 2013 [37] 12 44 22 42 10.2% 0.52 [0.30, 0.91]
Subtotal (95% CI) 474 470 56.2% 0.55 [0.29, 1.05]
Total events 165 203
Heterogeneity: Tau² = 0.55; Chi² = 35.91, df = 6 (P < 0.00001); I² = 83%
Test for overall effect: Z = 1.80 (P = 0.07)
Total (95% CI) 758 751 100.0% 0.60 [0.41, 0.87]
Total events 212 272
Heterogeneity: Tau² = 0.28; Chi² = 42.10, df = 13 (P < 0.0001); I² = 69%
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%
0.1
0.2
0.5
1
2
5
10
Favours experimental
Favours control

Figure 3

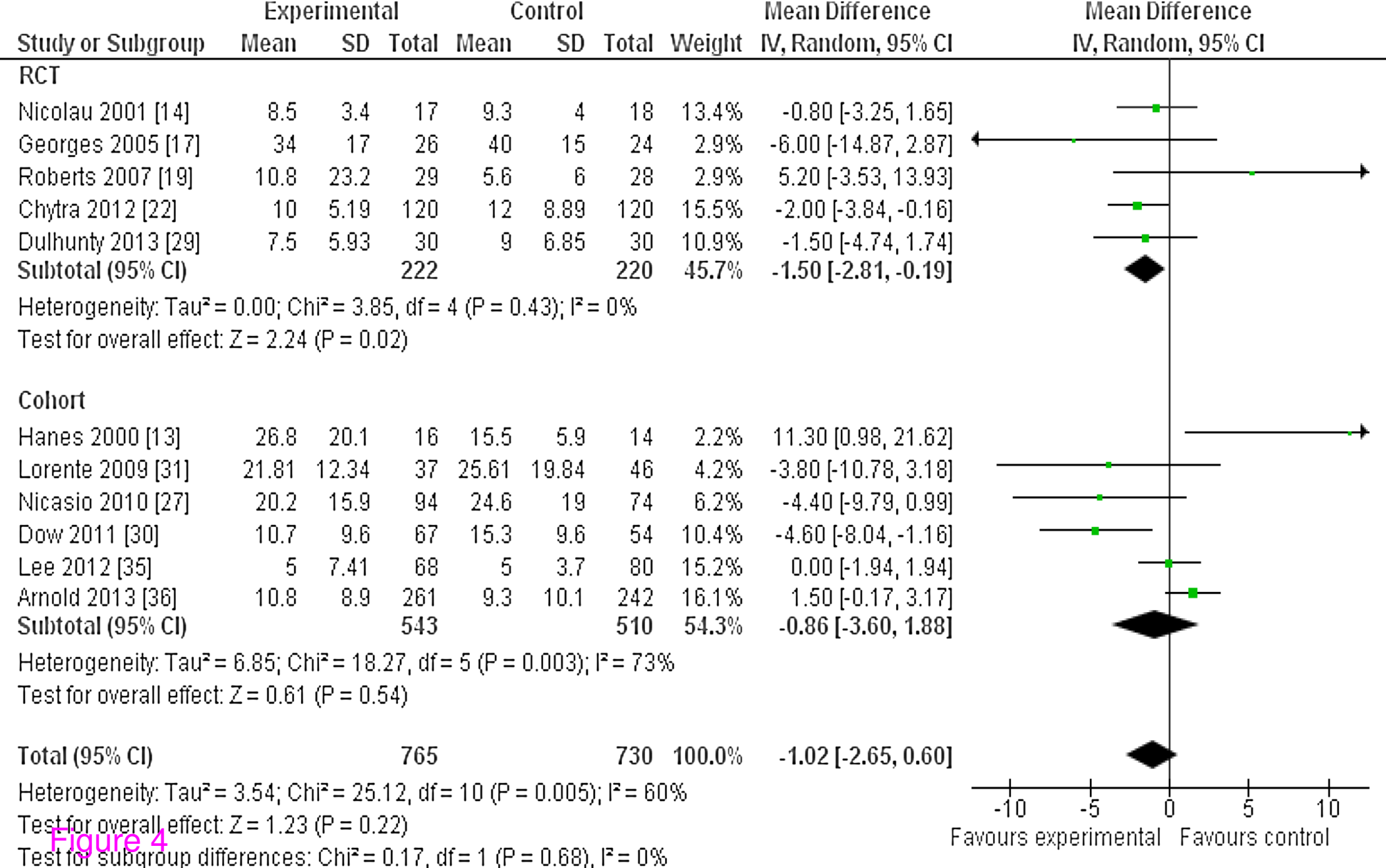
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
RCT
Nicolau 2001 [14] 8.5 3.4 17 9.3 4 18 13.4% -0.80 [-3.25, 1.65]
Georges 2005 [17] 34 17 26 40 15 24 2.9% -6.00 [-14.87, 2.87]
Roberts 2007 [19] 10.8 23.2 29 5.6 6 28 2.9% 5.20 [-3.53, 13.93]
Chytra 2012 [22] 10 5.19 120 12 8.89 120 15.5% -2.00 [-3.84, -0.16]
Dulhunty 2013 [29] 7.5 5.93 30 9 6.85 30 10.9% -1.50 [-4.74, 1.74]
Subtotal (95% CI) 222 220 45.7% -1.50 [-2.81, -0.19]
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.24 (P = 0.02)
Cohort
Hanes 2000 [13] 26.8 20.1 16 15.5 5.9 14 2.2% 11.30 [0.98, 21.62]
Lorente 2009 [31] 21.81 12.34 37 25.61 19.84 46 4.2% -3.80 [-10.78, 3.18]
Nicasio 2010 [27] 20.2 15.9 94 24.6 19 74 6.2% -4.40 [-9.79, 0.99]
Dow 2011 [30] 10.7 9.6 67 15.3 9.6 54 10.4% -4.60 [-8.04, -1.16]
Lee 2012 [35] 5 7.41 68 5 3.7 80 15.2% 0.00 [-1.94, 1.94]
Arnold 2013 [36] 10.8 8.9 261 9.3 10.1 242 16.1% 1.50 [-0.17, 3.17]
Subtotal (95% CI) 543 510 54.3% -0.86 [-3.60, 1.88]
Heterogeneity: Tau² = 6.85; Chi² = 18.27, df = 5 (P = 0.003); I² = 73%
Test for overall effect: Z = 0.61 (P = 0.54)
Total (95% CI) 765 730 100.0% -1.02 [-2.65, 0.60]
Heterogeneity: Tau² = 3.54; Chi² = 25.12, df = 10 (P = 0.005); I² = 60%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%
-10
-5
0
5
10
Favours experimental
Favours control

Figure 4

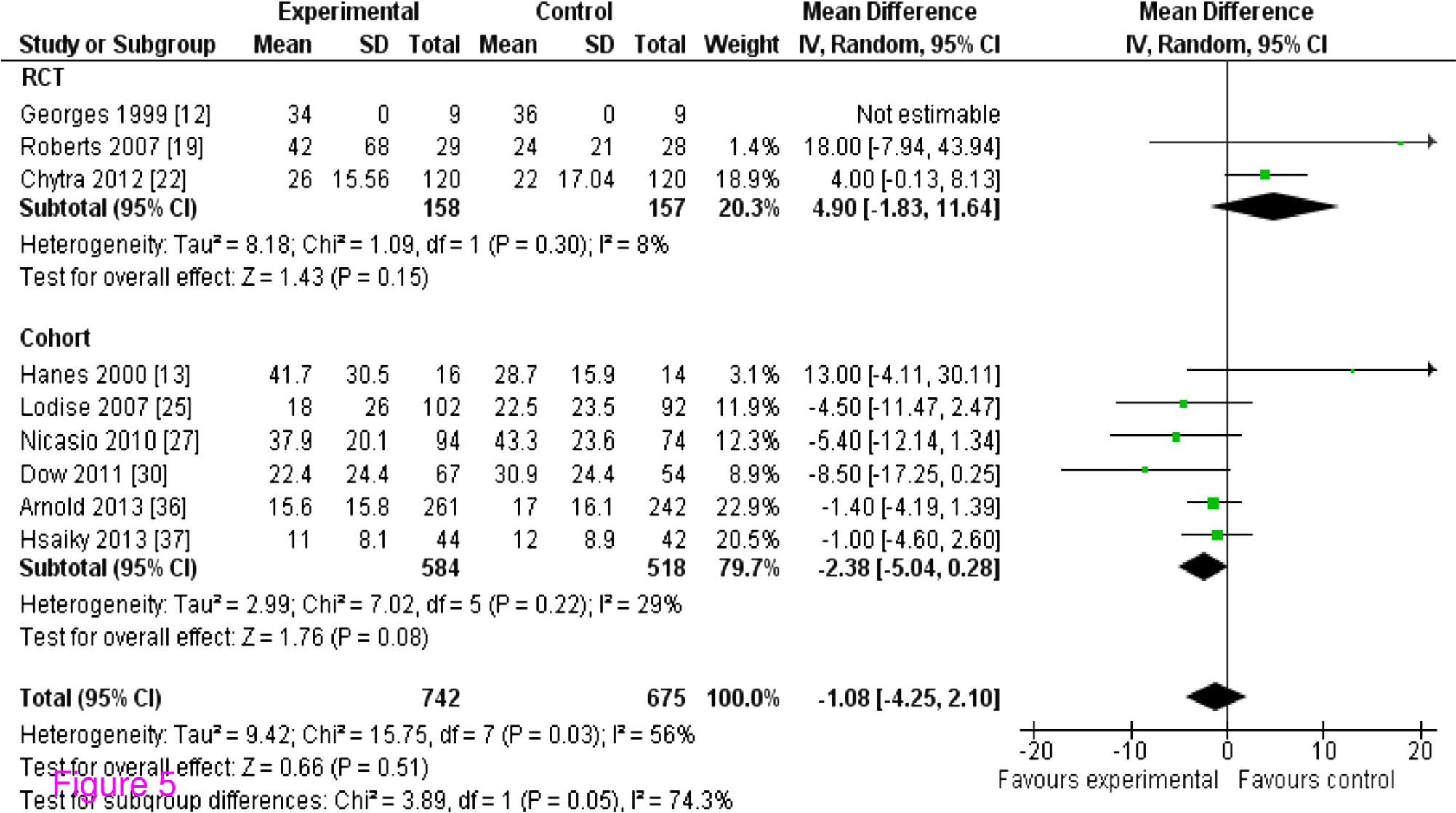
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup
Mean
SD
Total
Mean
SD
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
RCT
Georges 1999 [12] 34 0 9 36 0 9 Not estimable
Roberts 2007 [19] 42 68 29 24 21 28 1.4% 18.00 [-7.94, 43.94]
Chytra 2012 [22] 26 15.56 120 22 17.04 120 18.9% 4.00 [-0.13, 8.13]
Subtotal (95% CI) 158 157 20.3% 4.90 [-1.83, 11.64]
Heterogeneity: Tau² = 8.18; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%
Test for overall effect: Z = 1.43 (P = 0.15)
Cohort
Hanes 2000 [13] 41.7 30.5 16 28.7 15.9 14 3.1% 13.00 [-4.11, 30.11]
Lodise 2007 [25] 18 26 102 22.5 23.5 92 11.9% -4.50 [-11.47, 2.47]
Nicasio 2010 [27] 37.9 20.1 94 43.3 23.6 74 12.3% -5.40 [-12.14, 1.34]
Dow 2011 [30] 22.4 24.4 67 30.9 24.4 54 8.9% -8.50 [-17.25, 0.25]
Arnold 2013 [36] 15.6 15.8 261 17 16.1 242 22.9% -1.40 [-4.19, 1.39]
Hsaiky 2013 [37] 11 8.1 44 12 8.9 42 20.5% -1.00 [-4.60, 2.60]
Subtotal (95% CI) 584 518 79.7% -2.38 [-5.04, 0.28]
Heterogeneity: Tau² = 2.99; Chi² = 7.02, df = 5 (P = 0.22); I² = 29%
Test for overall effect: Z = 1.76 (P = 0.08)
Total (95% CI) 742 675 100.0% -1.08 [-4.25, 2.10]
Heterogeneity: Tau² = 9.42; Chi² = 15.75, df = 7 (P = 0.03); I² = 56%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Chi² = 3.89, df = 1 (P = 0.05), I² = 74.3%
-20
-10
0
10
20
Favours experimental
Favours control

Figure 5

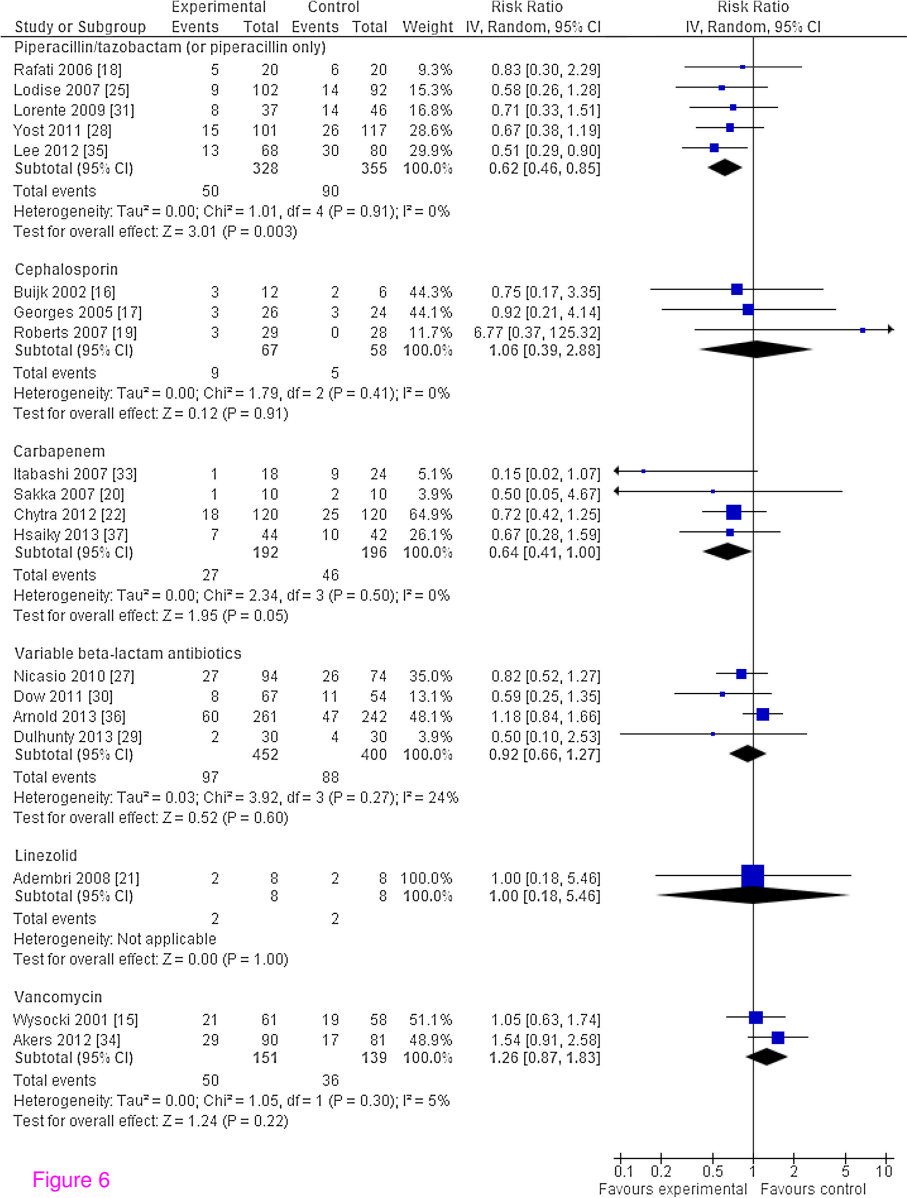
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Piperacillin/tazobactam (or piperacillin only)
Rafati 2006 [18] 5 20 6 20 9.3% 0.83 [0.30, 2.29]
Lodise 2007 [25] 9 102 14 92 15.3% 0.58 [0.26, 1.28]
Lorente 2009 [31] 8 37 14 46 16.8% 0.71 [0.33, 1.51]
Yost 2011 [28] 15 101 26 117 28.6% 0.67 [0.38, 1.19]
Lee 2012 [35] 13 68 30 80 29.9% 0.51 [0.29, 0.90]
Subtotal (95% CI) 328 355 100.0% 0.62 [0.46, 0.85]
Total events 50 90
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 4 (P = 0.91); I² = 0%
Test for overall effect: Z = 3.01 (P = 0.003)
Cephalosporin
Buijk 2002 [16] 3 12 2 6 44.3% 0.75 [0.17, 3.35]
Georges 2005 [17] 3 26 3 24 44.1% 0.92 [0.21, 4.14]
Roberts 2007 [19] 3 29 0 28 11.7% 6.77 [0.37, 125.32]
Subtotal (95% CI) 67 58 100.0% 1.06 [0.39, 2.88]
Total events 9 5
Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)
Carbapenem
Itabashi 2007 [33] 1 18 9 24 5.1% 0.15 [0.02, 1.07]
Sakka 2007 [20] 1 10 2 10 3.9% 0.50 [0.05, 4.67]
Chytra 2012 [22] 18 120 25 120 64.9% 0.72 [0.42, 1.25]
Hsaiky 2013 [37] 7 44 10 42 26.1% 0.67 [0.28, 1.59]
Subtotal (95% CI) 192 196 100.0% 0.64 [0.41, 1.00]
Total events 27 46
Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)
Variable beta-lactam antibiotics
Nicasio 2010 [27] 27 94 26 74 35.0% 0.82 [0.52, 1.27]
Dow 2011 [30] 8 67 11 54 13.1% 0.59 [0.25, 1.35]
Arnold 2013 [36] 60 261 47 242 48.1% 1.18 [0.84, 1.66]
Dulhunty 2013 [29] 2 30 4 30 3.9% 0.50 [0.10, 2.53]
Subtotal (95% CI) 452 400 100.0% 0.92 [0.66, 1.27]
Total events 97 88
Heterogeneity: Tau² = 0.03; Chi² = 3.92, df = 3 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.52 (P = 0.60)
Linezolid
Adembri 2008 [21] 2 8 2 8 100.0% 1.00 [0.18, 5.46]
Subtotal (95% CI) 8 8 100.0% 1.00 [0.18, 5.46]
Total events 2 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Vancomycin
Wysocki 2001 [15] 21 61 19 58 51.1% 1.05 [0.63, 1.74]
Akers 2012 [34] 29 90 17 81 48.9% 1.54 [0.91, 2.58]
Subtotal (95% CI) 151 139 100.0% 1.26 [0.87, 1.83]
Total events 50 36
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.30); I² = 5%
Test for overall effect: Z = 1.24 (P = 0.22)
0.1 0.2 0.5 1 2 5 10
Favours experimental Favours control

Figure 6

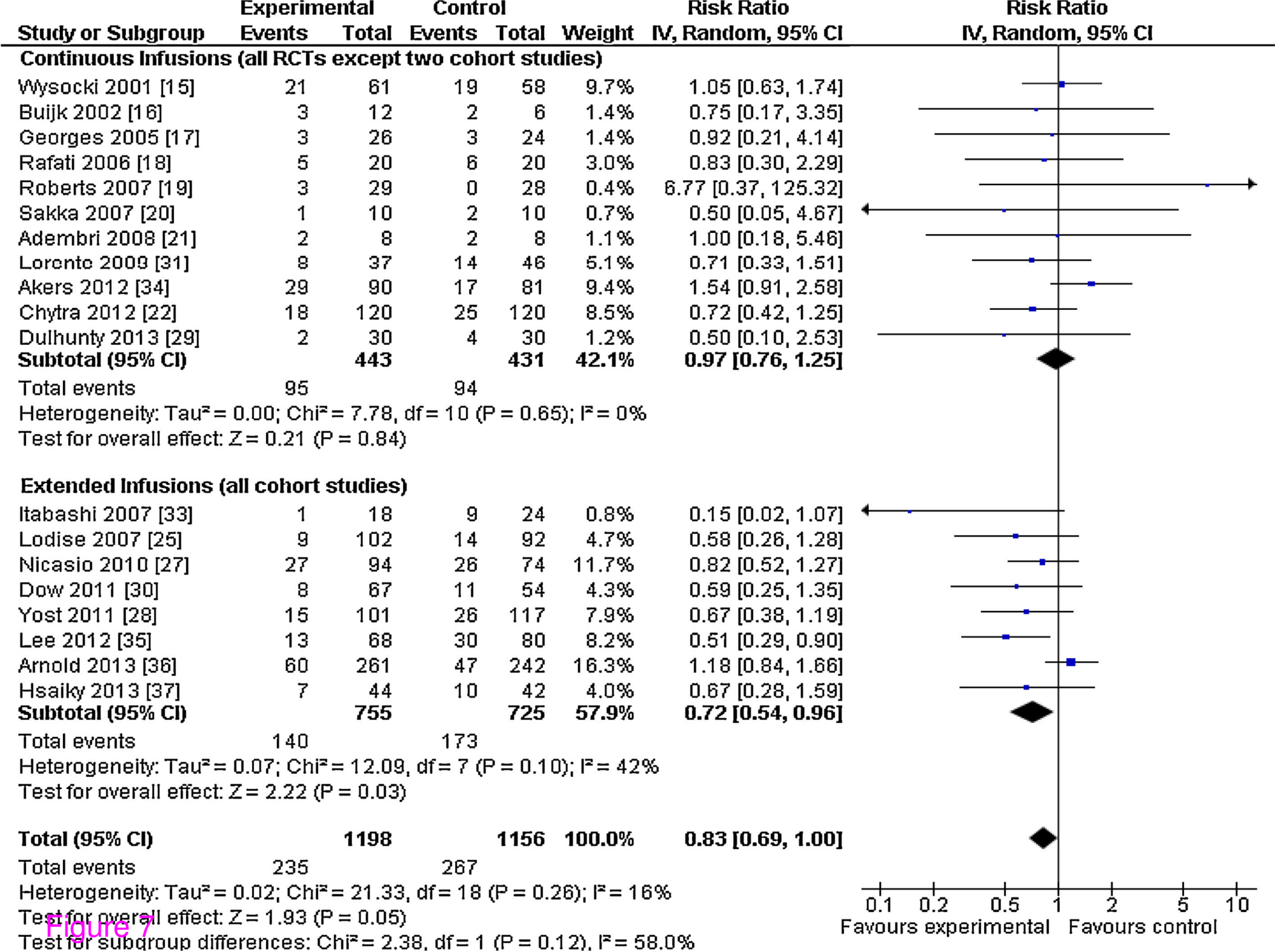
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
Continuous Infusions (all RCTs except two cohort studies)
Wysocki 2001 [15] 21 61 19 58 9.7% 1.05 [0.63, 1.74]
Buijk 2002 [16] 3 12 2 6 1.4% 0.75 [0.17, 3.35]
Georges 2005 [17] 3 26 3 24 1.4% 0.92 [0.21, 4.14]
Rafati 2006 [18] 5 20 6 20 3.0% 0.83 [0.30, 2.29]
Roberts 2007 [19] 3 29 0 28 0.4% 6.77 [0.37, 125.32]
Sakka 2007 [20] 1 10 2 10 0.7% 0.50 [0.05, 4.67]
Adembri 2008 [21] 2 8 2 8 1.1% 1.00 [0.18, 5.46]
Lorente 2009 [31] 8 37 14 46 5.1% 0.71 [0.33, 1.51]
Akers 2012 [34] 29 90 17 81 9.4% 1.54 [0.91, 2.58]
Chytra 2012 [22] 18 120 25 120 8.5% 0.72 [0.42, 1.25]
Dulhunty 2013 [29] 2 30 4 30 1.2% 0.50 [0.10, 2.53]
Subtotal (95% CI) 443 431 42.1% 0.97 [0.76, 1.25]
Total events 95 94
Heterogeneity: Tau² = 0.00; Chi² = 7.78, df = 10 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.84)
Extended Infusions (all cohort studies)
Itabashi 2007 [33] 1 18 9 24 0.8% 0.15 [0.02, 1.07]
Lodise 2007 [25] 9 102 14 92 4.7% 0.58 [0.26, 1.28]
Nicasio 2010 [27] 27 94 26 74 11.7% 0.82 [0.52, 1.27]
Dow 2011 [30] 8 67 11 54 4.3% 0.59 [0.25, 1.35]
Yost 2011 [28] 15 101 26 117 7.9% 0.67 [0.38, 1.19]
Lee 2012 [35] 13 68 30 80 8.2% 0.51 [0.29, 0.90]
Arnold 2013 [36] 60 261 47 242 16.3% 1.18 [0.84, 1.66]
Hsaiky 2013 [37] 7 44 10 42 4.0% 0.67 [0.28, 1.59]
Subtotal (95% CI) 755 725 57.9% 0.72 [0.54, 0.96]
Total events 140 173
Heterogeneity: Tau² = 0.07; Chi² = 12.09, df = 7 (P = 0.10); I² = 42%
Test for overall effect: Z = 2.22 (P = 0.03)
Total (95% CI) 1198 1156 100.0% 0.83 [0.69, 1.00]
Total events 235 267
Heterogeneity: Tau² = 0.02; Chi² = 21.33, df = 18 (P = 0.26); I² = 16%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Chi² = 2.38, df = 1 (P = 0.12), I² = 58.0%
0.1
0.2
0.5
1
2
5
10
Favours experimental
Favours control

Figure 7

Additional files provided with this submission:

Additional file 1: 1482225320104760_add1.pdf, 97K
http://ccforum.com/imedia/2418158551138962/supp1.pdf
Additional file 2: 1482225320104760_add2.pdf, 15K
http://ccforum.com/imedia/1840680423113896/supp2.pdf