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Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis (Review)

Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L

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[Intervention Review]

Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis

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ABSTRACT

Background

Optimal antibiotic treatment for sepsis is imperative. Combining a beta lactam antibiotic with an aminoglycoside antibiotic may provide certain advantages over beta lactam monotherapy.

Objectives

Our objectives were to compare beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy in patients with sepsis and to estimate the rate of adverse effects with each treatment regimen, including the development of bacterial resistance to antibiotics.

Search methods

In this updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 11); MEDLINE (1966 to 4 November 2013); EMBASE (1980 to November 2013); LILACS (1982 to November 2013); and conference proceedings of the Interscience Conference of Antimicrobial Agents and Chemotherapy (1995 to 2013). We scanned citations of all identified studies and contacted all corresponding authors. In our previous review, we searched the databases to July 2004.

Selection criteria

We included randomized and quasi-randomized trials comparing any beta lactam monotherapy versus any combination of a beta lactam with an aminoglycoside for sepsis.

Data collection and analysis

The primary outcome was all-cause mortality. Secondary outcomes included treatment failure, superinfections and adverse events. Two review authors independently collected data. We pooled risk ratios (RRs) with 95% confidence intervals (CIs) using the fixed-effect model. We extracted outcomes by intention-to-treat analysis whenever possible.

Main results

We included 69 trials that randomly assigned 7863 participants. Twenty-two trials compared the same beta lactam in both study arms, while the remaining trials compared different beta lactams using a broader-spectrum beta lactam in the monotherapy arm. In trials comparing the same beta lactam, we observed no difference between study groups with regard to all-cause mortality (RR 0.97, 95% CI 0.73 to 1.30) and clinical failure (RR 1.11, 95% CI 0.95 to 1.29). In studies comparing different beta lactams, we observed a trend for benefit with

monotherapy for all-cause mortality (RR 0.85, 95% CI 0.71 to 1.01) and a significant advantage for clinical failure (RR 0.75, 95% CI 0.67 to 0.84). No significant disparities emerged from subgroup and sensitivity analyses, including assessment of participants with Gram-negative infection. The subgroup of *Pseudomonas aeruginosa* infections was underpowered to examine effects. Results for mortality were classified as low quality of evidence mainly as the result of imprecision. Results for failure were classified as very low quality of evidence because of indirectness of the outcome and possible detection bias in non-blinded trials. We detected no differences in the rate of development of resistance. Nephrotoxicity was significantly less frequent with monotherapy (RR 0.30, 95% CI 0.23 to 0.39). We found no heterogeneity for all these comparisons.

We included a small subset of studies addressing participants with Gram-positive infection, mainly endocarditis. We identified no difference between monotherapy and combination therapy in these studies.

Authors' conclusions

The addition of an aminoglycoside to beta lactams for sepsis should be discouraged. All-cause mortality rates are unchanged. Combination treatment carries a significant risk of nephrotoxicity.

PLAIN LANGUAGE SUMMARY

A single beta lactam antibiotic versus a beta lactam-aminoglycoside combination for patients with severe infection

Infections caused by bacteria and requiring hospitalization are a leading cause of preventable death. The beta lactam antibiotics (e.g. penicillins, cephalosporins) and the aminoglycosides (e.g. gentamicin) kill bacteria by different means. Combining a beta lactam with an aminoglycoside could, therefore, result in more effective treatment of patients with severe infection but with the side effects of both antibiotics. We reviewed clinical trials that compared intravenous treatment with a beta lactam versus treatment with a beta lactam plus an aminoglycoside.

We searched the literature until November 2013. We included in the review 69 trials that randomly assigned 7863 participants. Participants were hospitalized with urinary tract, intra-abdominal, skin and soft tissue infections, pneumonia and infections of unknown source. One set of studies compared a broad-spectrum beta lactam versus a different, generally narrower-spectrum beta lactam combined with an aminoglycoside (47 studies). No clear difference in all-cause deaths was observed, but treatment failures were fewer with single beta lactam antibiotic treatment. A significant survival advantage was seen with single therapy in studies that involved infections of unknown source. The other studies compared one beta lactam versus the same beta lactam combined with an aminoglycoside antibiotic (22 studies). In these trials, no differences between single and combination antibiotic treatments were seen. Overall, adverse event rates did not differ between the study groups, but renal damage was more frequent with the combination therapy. Combination therapy did not prevent the development of secondary infection.

The review authors concluded that beta lactam-aminoglycoside combination therapy does not provide an advantage over beta lactams alone. Furthermore, combination therapy was associated with an increased risk of renal damage. The limited number of trials comparing the same beta lactam in both study arms and the fact that more than a third of the studies did not report on all-cause deaths may limit these conclusions. The subgroup of *Pseudomonas aeruginosa* infections was underpowered to examine effects.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Monotherapy versus combination therapy compared for sepsis

Monotherapy versus combination therapy compared for sepsis

Patient or population: participants with sepsis

Settings:

Intervention: monotherapy versus combination therapy

Comparison:

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Monotherapy versus combination therapy					
All-cause mortality—same beta lactam Survival Follow-up: mean 30 days ¹	Study population		RR 0.97 (0.73 to 1.3)	1431 (13 studies)	low ^{2,3}	
	112 per 1000	109 per 1000 (82 to 145)				
	High					
	300 per 1000	291 per 1000 (219 to 390)				
All-cause mortality—different beta lactam Follow-up: mean 30 days ¹	Study population		RR 0.85 (0.71 to 1.01)	4146 (31 studies)	low ^{3,4}	
	113 per 1000	96 per 1000 (80 to 114)				
	High					
	300 per 1000	255 per 1000 (213 to 303)				
Clinical failure—same beta lactam Antibiotic modifications Follow-up: two to 30 days ⁵	232 per 1000	258 per 1000 (221 to 300)	RR 1.11 (0.95 to 1.29)	1870 (20 studies)	very low ^{6,7}	
Clinical failure—different beta lactam Antibiotic modifications	227 per 1000	170 per 1000 (152 to 190)	RR 0.75 (0.67 to 0.84)	4933 (46 studies)	very low ^{6,7}	

Follow-up: two to 30 days⁵

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

Same and different beta lactams refer to comparisons involving the same beta lactam with versus without aminoglycoside and comparisons between one beta lactam versus a different beta lactam combined with an aminoglycoside, respectively.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Extracted preferentially at 30 days and if unavailable in-hospital or at end of follow-up.

²95% confidence intervals range from 27% improved survival to 30% higher risk of death with monotherapy.

³Funnel plot asymmetrical pointing out missing studies (unpublished or published but not reporting on mortality) favouring combination therapy.

⁴Advantage of monotherapy accentuated in studies with unclear allocation concealment and per-protocol analysis.

⁵Days after treatment cessation.

⁶Assessment of treatment failure in open trials prone to bias.

⁷Although this was the primary outcome in all studies, its clinical significance is unclear, and correlation with mortality is unclear (see discussion).

BACKGROUND

Description of the condition

Sepsis is defined as clinical evidence of infection, accompanied by a systemic inflammatory response such as fever. When associated with organ dysfunction, decreased blood flow in an organ (hypoperfusion) or abnormally low blood pressure (hypotension), sepsis is defined as severe (Bone 1992; Mandell 2004). Sepsis may be a response to direct microbial invasion or may be elicited by microbial signal molecules or toxin production. Bacterial infections may be lethal, with fatality rates ranging from less than 10% to more than 40% for those with severe sepsis (Moore 2001; Rangel-Frausto 1995; Russell 2000).

Description of the intervention

Antibiotic treatment for bacterial infection is usually initiated empirically, before the causative bacteria are identified and their susceptibility to antibiotic treatment is ascertained. Appropriate empirical antibiotic treatment, defined as that matching the in vitro susceptibility of subsequently identified bacteria, has been shown to halve the fatality associated with sepsis (Ibrahim 2000; Leibovici 1998; Paul 2010). Causative bacteria are identified only in about one-third of patients with sepsis overall (Paul 2006a). At this time, treatment is tailored according to the antibiotic susceptibilities of identified bacteria. Both empirically and after bacterial identification, single or combination antibiotic treatment may be given.

How the intervention might work

Combination antibiotic therapy offers several theoretical advantages. First, it can be used to broaden the spectrum of antibiotic coverage when used empirically to increase the chance of covering the causative bacteria. Second, the combination may possess an enhanced potential (synergism) when compared with the additive effect of each of the antibiotics assessed separately. Synergism between specific beta lactam antibiotics and aminoglycoside antibiotics has been shown in vitro for Gram-negative bacteria and specifically for *Pseudomonas aeruginosa* (Giamarellou 1986; Klastersky 1976; Klastersky 1982), *Staphylococcus aureus*, *Enterococcus* sp. and *Streptococcus* sp. (Bach 1980; Korzeniowski 1978; Levy 1979; Saleh-Mghir 1992; Sande 1974; Torres 1993). Third, combination therapy has been claimed to suppress the emergence of subpopulations of microorganisms resistant to antibiotics (Allan 1985; Milatovic 1987). Disadvantages of combination therapy may include additional costs, enhanced drug toxicity, possible induction of resistance caused by the broader antibiotic spectrum (Manian 1996; Weinstein 1985) and possible antagonism between specific drug combinations (Moellering 1986).

Why it is important to do this review

Several systematic reviews have addressed the clinical effects of beta lactam-aminoglycoside combinations for the treatment of sepsis, bacteraemia or specific types of infection. In previous versions of the current review (Paul 2003; Paul 2006), we found no advantage of combination therapy over monotherapy and an increased rate of renal toxicity with combination therapy. In a separate systematic review assessing the same intervention for cancer patients with neutropenia (excluded from the current review), similar results were found, with a small advantage of

monotherapy when compared with a narrower-spectrum beta lactam combined with an aminoglycoside (Paul 2013). To fully examine the implications of in vitro synergism, we pooled all randomized controlled trials comparing one beta lactam antibiotic versus the same beta lactam with an aminoglycoside (Marcus 2011). Overall, no advantage emerged for combination therapy; the subgroup of *P aeruginosa* bacteraemia was too small to allow definitive conclusions. Safdar et al. focused on Gram-negative bacteraemia and compiled randomized trials and observational studies (Safdar 2004). In the subgroup of *P aeruginosa* bacteraemia, an advantage was reported for combination therapy, but aminoglycosides were used as monotherapy in some of the trials (Paul 2005). Kumar et al. performed a meta-regression analysis showing that an advantage of combination therapy involved mortality rates in randomized and observational studies (Kumar 2010), but how much of this was due to the inherent association between odds ratios and event rates and how much to a true clinical effect was unclear (Paul 2010a). When restricting the analysis to infective endocarditis (caused by Gram-positive bacteria), Falagas et al. found no advantage of combination therapy (Falagas 2006). The same group of authors reported no advantage of combination therapy with regard to emergence of antibiotic resistance following therapy (Bliziotis 2005).

Despite the large body of evidence pointing against a benefit for combination therapy, most recommendations and guidelines still recommend combination therapy, and combination therapy is frequently used in clinical practice. In the guidelines for the management of severe sepsis of the "Surviving Sepsis Campaign", initial combination therapy is recommended (Dellinger 2008). Narrowing the spectrum of coverage after three to five days is recommended, except for infections caused by *P aeruginosa* and infections among neutropenic patients, for whom continued combination treatment is advised. Beta lactam-aminoglycoside treatment is recommended for pneumonia caused by *P aeruginosa* (Sun 2011). Treatment of infective endocarditis has traditionally consisted of beta lactam-aminoglycoside combinations based on in vitro synergy studies and experimental studies. Although current guidelines, acknowledging the lack of evidence, recommend beta lactam monotherapy as first-line therapy for most pathogens, combination therapy is still suggested as optional treatment and is recommended for resistant bacteria, mainly *Enterococcus* sp. and *S aureus* (Baddour 2005).

OBJECTIVES

Our objectives were to compare beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy in patients with sepsis and to estimate the rate of adverse effects with each treatment regimen, including the development of bacterial resistance to antibiotics.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized or quasi-randomized controlled trials.

Types of participants

We included hospitalized participants with sepsis acquired in the community or in the hospital. We defined sepsis as clinical evidence

of infection plus evidence of a systemic response to infection (Bone 1992). We excluded neonates and preterm babies. We also excluded studies including more than 15% neutropenic patients.

Types of interventions

We considered studies comparing the antibiotic regimens described below.

1. Any intravenous beta lactam antibiotic given as monotherapy, including:
 - a. penicillins;
 - b. beta lactam drugs plus beta lactamase inhibitors (e.g. co-amoxiclav);
 - c. cephalosporins (e.g. ceftazidime, cefotaxime); or
 - d. carbapenems (e.g. imipenem, meropenem).
2. Combination therapy of a beta lactam antibiotic (as specified) with one of the following aminoglycoside antibiotics:
 - a. gentamicin;
 - b. tobramycin;
 - c. amikacin;
 - d. netilmicin;
 - e. streptomycin;
 - f. isepamicin; or
 - g. sisomicin.

Types of outcome measures

Primary outcomes

All-cause mortality by the end of the study follow-up.

Secondary outcomes

1. Treatment failure defined as death and/or one or more serious morbid events (persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any modification of the assigned empirical antibiotic treatment; or any therapeutic invasive intervention required and not defined in the protocol). If defined differently, the study definitions were documented.
2. Length of hospital stay.
3. Superinfection: recurrent infections, defined as new, persistent or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen (different pathogen or same pathogen with different susceptibilities) or the development of a new site of infection.
4. Colonization by resistant bacteria: the isolation of bacteria resistant to the beta lactam antibiotic, during or following antibiotic therapy, with no signs or symptoms of infection.
5. Adverse effects:
 - a. life-threatening or associated with permanent disability (severe nephrotoxicity; ototoxicity; anaphylaxis; severe skin reactions);
 - b. serious: requiring discontinuation of therapy (other nephrotoxicity; seizures; pseudomembranous colitis; other allergic reactions); or
 - c. any other (other gastrointestinal; other allergic reactions).

Search methods for identification of studies

Electronic searches

We formulated a comprehensive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

We searched the Cochrane Infectious Diseases Group specialized trials register for relevant trials up to September 2011 using the following search terms: ((aminoglycoside* OR netilmicin* OR gentamicin* OR amikacin* OR tobramycin* OR streptomycin* OR isepamicin* OR sisomicin*) AND (pneumonia* OR infection OR infect* OR sepsis OR bacter* OR bacteremia OR septicemia)).

In this updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2013, Issue 11; see [Appendix 1](#) for a detailed search strategy), PubMed (1966 to November 2013; see [Appendix 2](#)), EMBASE (Ovid SP, 1980 to November 2013; see [Appendix 3](#)) and LILACS (via BIREME interface, 1982 to November 2013; see [Appendix 4](#)). We combined our PubMed search strategy with the Cochrane highly sensitive search strategy for identifying randomized controlled trials (RCTs), as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We modified this RCT filter for use in EMBASE and LILACS. In our previous review (Paul 2006), we searched the databases until July 2004.

Searching other resources

We searched the Interscience Conference of Antimicrobial Agents and Chemotherapy conference proceedings (1995 to 2012) and the European Congress of Clinical Microbiology and Infectious Diseases (2000 to 2013) for relevant abstracts.

We contacted the first or corresponding author of each included study and researchers active in the field for information regarding unpublished trials or for complementary information on their own trials.

We also checked the citations of major reviews and of all trials identified by the above methods for additional studies.

We did not have a language restriction.

Data collection and analysis

Selection of studies

One review author (MP for the original review; AL for the 2013 update) inspected the abstract of each reference identified in the search and applied the inclusion criteria. When relevant articles were identified, the full article was obtained and was inspected independently by two review authors (MP, AL, IS or LL).

Data extraction and management

Two review authors (MP, Ishay Silbiger or SG-G) independently extracted data from included trials in the original review, and AL and MP extracted data for the 2012 update. In case of disagreement between the two review authors, a third review author (LL) independently extracted the data. A third review author (LL) also extracted the data in 10% of the studies, selected at random. We discussed data extraction, documented decisions and contacted authors of all studies for clarification. We resolved differences in the

data extracted by discussion. We also documented the justification for excluding studies from the review.

We identified the trials by the name of the first author and the year in which the trial was first published, and we listed them in chronological order. We extracted, checked and recorded the following data.

Characteristics of trials

1. Date, location and setting of trial.
2. Publication status.
3. Country of origin.
4. Design (intention-to-treat, method of randomization).
5. Duration of study follow-up.
6. Performance of surveillance cultures (routine cultures for the detection of colonization).
7. Sponsor of trial.

Characteristics of participants

1. Number of participants in each group.
2. Age (mean and standard deviation, or median and range).
3. Number of participants with renal failure before treatment.
4. Number of participants with shock.

Characteristics of infection

1. Number of participants with infection caused by bacteria resistant to the administered beta lactam antibiotic.
2. Number of participants with nosocomial infection.
3. Number of participants with bacteraemia.
4. Number of participants with bacteriologically documented infection.
5. Number of participants with infection caused by Gram-negative bacteria.
6. Number of participants with Gram-negative bacteraemia.
7. Number of participants with documented *Pseudomonas* infection (*Pseudomonas* isolated in blood or specimen(s) obtained from suspected site(s) of infection).
8. Number of participants with:
 - a. urinary tract infection;
 - b. pneumonia;
 - c. intra-abdominal infection;
 - d. skin and soft tissue infection; and
 - e. infection of unknown origin.

Characteristics of interventions

1. Antibiotic type and dose.
2. Duration of therapy (mean).

Characteristics of outcome measures

1. Number of deaths at the end of the follow-up period.
2. Number of participants failing treatment (as defined).
3. Adverse reactions (as defined) in each group.
4. Loss of follow-up (dropouts) before the end of the study in each group.
5. Number of participants developing superinfection.

6. Number of participants developing colonization (as defined) with resistant bacteria.
7. Duration of fever and hospital stay.

We collected outcome measures on an intention-to-treat basis whenever possible. When such data were not presented, we sought information from the trial authors, and, if unavailable, per-protocol results were used. For failure outcome, we performed sensitivity analyses comparing these results with a 'presumed all intention to treat', which we achieved by counting all dropouts as failures. We could not make such an assumption in studies that did not specify the number of dropouts per study arm, and we analysed these studies separately.

Assessment of risk of bias in included studies

We assessed the risk of bias of the trials to be included for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, blinding and incomplete outcome data (for mortality and failure outcomes), selective reporting, intention-to-treat analysis and number of participants excluded from the outcome assessment. Two review authors (MP, AL, Ishay Silbiger and Karla Soares-Weiser) independently performed the risk of bias assessment by classifying each item separately as low, unclear or high risk of bias according to the criteria suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We calculated risk ratios for dichotomous outcomes. For length of stay, we extracted the measure reported in the study (mean or median) along with its dispersion measure.

Unit of analysis issues

We expected all studies to be individually randomly assigned and to recruit each participant only once into the trial; thus no unit of analysis issues were expected for this review.

Dealing with missing data

We contacted the first or corresponding author of each included study and researchers active in the field to ask for information regarding unpublished trials or complementary information on their own trials.

Assessment of heterogeneity

We initially assessed heterogeneity by visual inspection of the forest plots. Statistical assessment was based on the Chi² test of heterogeneity ($P < 0.1$) and the I² measure of inconsistency (substantial and considerable heterogeneity $> 50\%$) (Higgins 2011).

Assessment of reporting biases

We visually examined a funnel plot of standard error (SE) (log(risk ratio)) versus risk ratio of each study to estimate small study effects, including publication bias or other. Statistical testing for funnel plot asymmetry was conducted using Egger's regression (Comprehensive Meta Analysis, version 2.2). The funnel plot was examined for the outcomes of mortality and failure.

Data synthesis

We used the Mantel-Haenszel fixed-effect model to pool risk ratios. We did not plan to pool results for length of stay because this variable is not normally distributed.

Subgroup analysis and investigation of heterogeneity

We explored heterogeneity by subgroup analysis of the different types of infection.

1. Infections caused by Gram-negative bacteria and *P aeruginosa*.
2. Gram-negative bacteraemia.
3. Urinary tract infection and non-urinary tract infection, assuming that the latter might be more serious and thus might benefit more from combination therapy.
4. Gram-positive infection and endocarditis.

For subgroup analyses, we analysed the outcomes of mortality and failure. For Gram-positive infection, we also analysed microbiological failure.

Sensitivity analysis

We analysed separately studies at low risk of bias with regard to allocation concealment, generation, blinding and incomplete

outcome data reporting. We based conclusions regarding the effect of risk of bias on results on the evidence of a strong association between poor allocation concealment and overestimation of effect (Schulz 1995).

RESULTS

Description of studies

Results of the search

The search strategy resulted in 6562 references. We filtered double references and screened 3629 different abstracts for inclusion. We did not further evaluate studies in which the comparator antibiotic regimens were clearly incompatible with inclusion criteria. We similarly excluded non-randomized and non-human studies. We retrieved 159 studies for full-text inspection, of which we excluded 72 publications. Eighty-three articles were deemed eligible for inclusion, of which 14 were secondary publications. One is ongoing (Characteristics of ongoing studies); thus we have included 69 trials in this review (Figure 1). Five trials are included in the current update that were not included in the original review (Banasal 2006; Damas 2006; Hasali 2005; Figueroa-Damian 1996; García Ramírez 1999).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

Main study characteristics are detailed in the table [Characteristics of included studies](#). The included studies were performed between the years 1968 and 2006. Twenty-two were multi-centred. Twenty-one were performed in the United States or Canada, 35 in Europe and 14 in other countries. The studies included 7863 participants. The median number of included participants per trial was 80 (range 20 to 580). Four trials ([Banasal 2006](#), [Cardozo 2001](#); [Hasali 2005](#), [Naime Libien 1992](#)) included children, and all other trials were restricted to or included mostly adults.

The studies differed by the type of population and the type of infection targeted (see [Characteristics of included studies](#)). Forty-five trials included participants with severe sepsis, suspected Gram-negative infection or pneumonia (designated as 'sepsis'). The adjusted mean fatality rate in these studies was 8.5%. Twelve trials included participants with intra-abdominal infection, related

mainly to the biliary tract (designated 'abdominal'). The mean fatality rate in these trials was 1.7%. Seven trials were restricted to participants with urinary tract infection (UTI), all hospitalized, mainly women. Five of these studies reported on mortality, and no deaths occurred in four. Finally, five of the studies included in the review targeted participants with Gram-positive infection. Four studies addressed participants with endocarditis caused by *S aureus* ([Abrams 1979](#); [Korzeniowski 1982](#); [Ribera 1996](#)) or streptococci ([Sexton 1998](#)). One study included any staphylococcal infection ([Coppens 1983](#)).

Most studies compared beta-lactam monotherapy vs. beta-lactam-aminoglycoside combination therapy as the initial, empirical antibiotic treatment administered to participants. Four studies assessed the empirical and definitive treatment of a specific infection by randomly assigning participants empirically and evaluating only those who subsequently fulfilled criteria for

the specific infection. Two such studies randomly assigned participants with suspected endocarditis and evaluated only those with *S aureus* bacteraemia and proven endocarditis (Abrams 1979; Korzeniowski 1982). The other two randomly assigned participants with suspected biliary tract infection and evaluated only participants with a surgically proven diagnosis (Gerecht 1989; Yellin 1993). Non-evaluated participants in these studies were not counted as dropouts because the study protocol a priori defined evaluation only for participants fulfilling definitive criteria. Eight studies, focusing on participants with specific infections or pathogens (e.g. cholecystitis, staphylococcal infections), tested the effect of monotherapy versus combination therapy semi-empirically. In these studies (designated 'semi-empirical', see [Characteristics of included studies](#)), randomization occurred after the specific infection was documented and participants could have received prior antibiotic treatment for this infection. Analysis of empirical and semi-empirical studies was not separated.

The specific antibiotic regimens used are detailed in the table [Characteristics of included studies](#). Forty-seven studies compared a single beta lactam drug versus a different, narrower-spectrum beta lactam combined with an aminoglycoside (designated 'different BL'). Sixteen 'different BL' studies reported baseline susceptibility rates of the pathogens isolated on admission to the beta lactam. The beta lactam used in the combination arm covered fewer pathogens than the monotherapy beta lactam in 13 studies, and the opposite occurred in two studies only. Twenty-two studies compared the same beta lactam in the combination

and monotherapy arms (designated 'same BL'). Results obtained from studies comparing same and different beta lactams were kept separated throughout all efficacy analyses. The beta lactam monotherapies used in the studies and their dosing are detailed in [Table 1](#). The aminoglycoside was administered once daily in nine trials (Cardozo 2001; Damas 2006; García Ramírez 1999; Hasali 2005; Jaspers 1998; Rubinstein 1995; Sandberg 1997; Sexton 1998; Speich 1998). Other trials administered the aminoglycosides multiple times daily (49 trials) or did not specify the administration schedule (11 trials). Mean antibiotic treatment duration ranged between three and 17.5 days in the sepsis studies, between 6.8 and 11.9 days in the abdominal studies, between 4.1 and seven days in the UTI studies and between two and four weeks in the endocarditis studies.

Excluded studies

We excluded 72 publications, representing 69 studies ([Figure 1; Characteristics of excluded studies](#)). Several studies compared monotherapy versus combination therapy among participants with cystic fibrosis. Participants in these studies typically did not have fever or other signs of sepsis when entering the trial and thus did not fulfil inclusion criteria for this review. These studies are included in a separate review (Elphick 2005).

Risk of bias in included studies

See [Characteristics of included studies](#), Risk of bias tables, [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias): Mortality	Incomplete outcome data (attrition bias): Failure	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Abrams 1979	?	?	-	-	?	-	-
Aguilar 1992	?	?	?	+	?	-	-
Alvarez-Lerma 2001a	+	+	+	-	?	-	-
Arich 1987	+	+	-	-	?	-	-
Banasal 2006	+	+	?	+	?	-	-
Bergeron 1988	?	?	-	-	?	-	-
Biglino 1991	?	?	?	+	?	-	-
Brown 1984	+	?	-	-	?	-	+
Carbon 1987	?	?	+	+	?	-	-
Cardozo 2001	?	?	+	+	?	-	-
Cometta 1994	+	+	-	-	?	-	-
Cone 1985	?	?	-	-	?	-	-
Coppens 1983	+	?	?	-	?	-	-
D'Antonio 1992	+	+	+	-	?	-	-
Damas 2006	?	?	+	?	?	-	-
Duff 1982	-	-	+	?	?	-	-
Dupont 2000	+	+	?	?	?	-	+
Felisart 1985	+	?	?	?	?	-	-
Figuroa-Damian 1996	?	?	?	+	?	-	-
Finer 1992	+	+	-	-	?	-	-

Figure 3. (Continued)

Finer 1992	+	+	-	-	?	-	-
García Ramírez 1999	-	-	+	+		-	-
Gerecht 1989	+	?	?	+	?	-	-
Gomez 1990a	+	+	-	-	?	-	-
Hasali 2005	-	-	?	?	?	-	-
Havig 1973	+	?	-	-	?	-	-
Hoepelman 1988	?	+	+	+	?	-	-
Holloway 1985	?	?	?	-	?	-	-
Iakovlev 1998	?	?	?	+	?	-	-
Jaspers 1998	+	+	+	+	?	-	-
Klastersky 1973	?	?	-	-	?	-	-
Kljucar 1990	+	+	+	+	?	-	-
Koehler 1990	?	?	+	-	?	-	-
Korzeniowski 1982	+	+	-	-	?	-	-
Landau 1990	-	-	+	+	?	-	-
Limson 1988	?	?	?	-	?	-	-
Mandell 1987	+	?	?	-	?	-	-
Martin 1991	+	?	?	?	?	-	-
McCormick 1997	+	+	-	-	?	-	-
Mergoni 1987	?	+	?	+	?	-	-
Moreno 1997	?	?	?	-	?	-	-
Mouton 1990	?	?	+	+	?	-	-
Mouton 1995	?	?	+	-	?	-	-
Muller 1987	+	?	?	-	?	-	-
Naime Libien 1992	?	?	+	+	?	-	-
Piccart 1984	?	?	?	-	?	-	-
Rapp 1984	?	?	?	+	?	-	-
Rasmussen 1986	+	?	-	-	?	-	-
Ribera 1996	+	+	+	+	?	-	-
Rubinstein 1995	+	+	+	-	?	-	+
Sage 1987	?	?	?	-	?	-	-

Figure 3. (Continued)

Sage 1987	?	?	?	-	?	-	-
Sandberg 1997	+	+	+	-	?	-	-
Sanfilippo 1989	+	+	?	+	?	+	+
Sculier 1982	?	?	+	+	?	-	-
Sexton 1998	?	?	?	-	?	-	-
Sieger 1997	?	?	+	+	?	-	-
Smith 1984	+	+	-	-	?	+	+
Speich 1998	+	+	+	-	?	-	-
Stille 1992	+	?	?	?	?	-	-
Sukoh 1994	?	?	?	+	?	-	-
Takamoto 1994	+	?	?	-	?	-	-
Thompson 1990	+	?	-	-	?	-	-
Thompson 1993	+	?	-	-	?	-	-
Trujillo 1992	?	?	?	?	?	-	-
Vergnon 1985	+	?	?	+	?	-	-
Verzasconi 1995	?	?	?	-	?	-	-
Warren 1983	+	?	-	-	?	-	-
Wiecek 1986	?	?	+	+	?	-	-
Wing 1998	+	+	+	+	?	-	-
Yellin 1993	+	+	-	-	?	-	+

Allocation

Thirty-two percent of the studies (22/69) reported adequate allocation concealment and thus considered were at low risk of bias. Four studies were graded as high risk of bias (Duff 1982; García Ramírez 1999; Hasali 2005; Landau 1990). No information was available for the other studies (37 studies), or envelopes were used but were not described as sealed or opaque (six studies).

Allocation generation was considered at low risk of bias in 51% of the studies (35/69). No information was available for 30 studies. Two studies were at high risk of bias, using participant identification numbers (Duff 1982; Landau 1990). Both allocation generation and concealment were at low risk in 29% of the studies (20/69).

Blinding

Most studies were open. Although these were considered at high risk of bias, for mortality assessment the lack of blinding after randomization probably did not introduce bias. Two studies, including 226 participants, were double-blinded (Sanfilippo 1989;

Smith 1984). Outcome assessors were blinded in four studies (Brown 1984; Dupont 2000; Rubinstein 1995; Verzasconi 1995). Clinicians were blinded to treatment in one study (Yellin 1993).

Incomplete outcome data

We separated included studies into four different study types with relation to outcome reporting.

1. Full Intention-to-treat analysis (all randomly assigned participants included in the analysis).
2. Per-protocol analysis, in which the number of dropouts was given per study arm.
3. Per-protocol analysis, in which the number of dropouts was known but was not given per study arm.
4. Studies that did not distinguish between the number of randomly assigned participants and the number of evaluated participants. These studies did not refer to dropouts, but the study authors did not define the study explicitly as intention-to-treat.

The distribution of included studies by study type was as follows.

- All-cause fatality (reported in 44 studies).
 - Type one: 20 studies (45%).
 - Types two and three: 18 studies (41%).
 - Type four: six studies (14%).
- Treatment failure (reported in 66 studies).
 - Type one: 15 studies (23%).
 - Type two: 23 studies (37%).
 - Type three: 16 studies (25%).
 - Type four: 12 studies (18%).

Selective reporting

Protocols were not available for most studies because they were conducted before mandatory trial registry. In general, the primary outcome specified as planned and reported in all trials was "treatment success" (a variously defined composite outcome including clinical response and the need for antibiotic modifications). All-cause mortality was not specifically defined as an outcome in most trials, and if reported, it was a safety measure reported in the results. Since this was uniformly observed across trials, we have not specified selective reporting for each trial in the Risk of bias tables.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

See: [Summary of findings for the main comparison Monotherapy versus combination therapy compared for sepsis](#)

All-cause mortality

Forty-four trials including 5577 participants were included in this comparison ([Analysis 1.1](#)). Thirteen studies including 1431 participants compared the same beta lactam. These studies showed near equivalence (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.73 to 1.30), and studies comparing different beta lactams tended non-significantly in favour of monotherapy (RR 0.85, 95% CI 0.71 to 1.01). No heterogeneity was present for these comparisons ($I^2 = 0\%$ for the same beta lactam comparison, $I^2 = 19\%$ for different beta lactams). Analysis was further broken down according to the main study population, excluding Gram-positive infection studies ([Analysis 1.2](#)). The advantage of the monotherapy was statistically significant in studies comparing different beta lactams addressing 'sepsis' (RR 0.83, 95% CI 0.69 to 0.99), but no significant differences were noted between subgroups in this analysis.

The funnel plot analysis for all-cause mortality showed that small studies favouring combination therapy may be missing ([Figure 4](#); Egger's regression two-sided P value 0.05). Mortality outcome was unavailable from 36% of the trials.

Figure 4. Funnel mortality. All-cause mortality.

Subgroup analyses

No significant difference between monotherapy and combination therapy was apparent when analysis was restricted to participants

with any Gram-negative infection (eight studies) or Gram-negative bacteraemia (five studies; [Analysis 2.1](#); [Analysis 2.2](#)). Only four studies permitted mortality outcome extraction among participants with *P aeruginosa* infection, and these did not show a

difference (total of 60 evaluable participants and 15 deaths; graph not shown). Five UTI studies reported mortality, and mortality was null in three studies. Excluding participants with UTI from the analysis ('non-UTI' subgroup; [Analysis 2.3](#)) strengthened the advantage of monotherapy in studies comparing different beta lactams (RR 0.70, 95% CI 0.52 to 0.95).

Three studies addressing Gram-positive infection reported on mortality, all comparing the same antibiotics, with a small sample size and few deaths ([Analysis 2.4](#)). No difference was observed between monotherapy and combination therapy, with the point estimate in the direction favouring monotherapy (RR 0.44, 95% CI 0.12 to 1.58).

Sensitivity analyses

Low-risk allocation concealment and generation were associated with risk ratios closer to one than studies with unclear methods for studies comparing different beta lactams but without a statistically significant difference between subgroups ([Analysis 3.1](#); [Analysis 3.2](#)). Combination therapy was significantly better among studies comparing different beta lactams classified as unclear allocation concealment. Blinding was performed in too few studies to assess its effect on mortality. The combined RR for studies comparing the same beta lactam and reporting mortality by intention-to-treat was 0.57 (95% CI 0.28 to 1.19) compared with 1.09 (95% CI 0.80 to 1.51) for studies reporting mortality per-protocol ([Analysis 3.3](#); P value 0.11 for subgroup difference). Comparison of intention-to-

treat versus per-protocol studies for different beta lactams did not reveal a difference. Reanalysis of the mortality comparison by the random-effects model was very similar for same beta lactams (RR 0.99, 95% CI 0.74 to 1.33) and for different beta lactams (RR 0.85, 95% CI 0.69 to 1.05).

Treatment failure

We included 66 trials in the clinical failure analysis, comprising 6803 participants ([Analysis 1.3](#)). We detected no difference between monotherapy and combination therapy among studies comparing the same beta lactam (RR 1.11, 95% CI 0.95 to 1.29). We found a significant advantage of monotherapy among studies comparing different beta lactams (RR 0.75, 95% CI 0.67 to 0.84). No heterogeneity was present ($I^2 = 0\%$ for both comparisons). Grouping studies according to study population highlighted an advantage of combination therapy among the 'sepsis' studies that compared the same beta lactam (RR 1.25, 95% CI 1.01 to 1.55). This group of studies also accentuated the opposing advantage of monotherapy among studies comparing different beta lactams ([Analysis 1.4](#)). Assessment of efficacy for urinary tract infection included reinfection and relapse as outcomes ([Analysis 1.5](#)). We noted no significant difference between monotherapy and combination therapy, with six trials and 458 participants included in this comparison.

The funnel plot for treatment failure generated a nearly symmetrical 'funnel distribution' ([Figure 5](#)).

Figure 5. Funnel failure.

Subgroup analyses

We analysed 28 studies including 1835 participants with Gram-negative infection and 18 studies including 426 participants with *P aeruginosa* infection (Analysis 2.5; Analysis 2.6). We observed no significant differences between the study groups for studies comparing the same or different beta lactams. For studies comparing the same beta lactam, the RR was 1.23 (95% CI 0.90 to 1.68) for Gram-negative infection and 1.02 (95% CI 0.68 to 1.51) for *P aeruginosa* infection. We observed no difference between study groups among participants with Gram-negative bacteraemia or any bacteraemia (Analysis 2.7; Analysis 2.8). The latter comparison mainly comprised participants with Gram-negative bacteraemia but was available from a larger number of studies and showed a large advantage of monotherapy among studies comparing different beta lactams. Both subgroups of participants with UTIs (Analysis 2.9) and participants without UTIs maintained the trends seen previously (Analysis 2.10).

All five studies targeting Gram-positive infection reported on clinical failure. All compared the same beta lactam. The combined risk ratio for clinical failure was 0.69 (95% CI 0.40 to 1.19, five studies, 305 participants; Analysis 2.11). Measures of treatment failure in these studies included persistence of bacteraemia or signs of endocarditis, relapse, need for valve replacement, need for surgery in endocarditis and death. The time of outcome determination was predefined in all trials and follow-up was long (one to six months). The need for surgery in endocarditis was reported in all four trials including participants with endocarditis, with no statistically significant difference noted between treatment groups (Analysis 2.12).

Sensitivity analyses

The quality of allocation concealment and generation did not affect the risk ratios for treatment failure among studies comparing the same or different beta lactams (Analysis 3.4; Analysis 3.5). All studies at high risk for bias (quasi-randomized) compared different beta lactams, and their results were highly heterogeneous.

Several studies comparing different beta lactams used some type of blinding. The advantage of monotherapy was non-significantly larger among these studies compared with non-blinded studies (Analysis 3.6; P value 0.05 for subgroup difference).

Among studies comparing the same beta lactam, we observed an advantage of combination therapy in the presumed intention-to-treat analysis (type two studies), in which we imputed failure for dropouts. Among studies comparing different beta lactams, intention-to-treat, presumed intention-to-treat and per-protocol results were similar, favouring monotherapy (Analysis 3.7). Analysis by the random-effects model did not change the results (RR 1.09, 95% CI 0.94 to 1.27 for same beta lactams; RR 0.76, 95% CI 0.67 to 0.87 for different beta lactams).

Bacteriological cure

Bacteriological cure occurred more frequently with monotherapy among studies comparing different beta lactams (RR 0.81, 95% CI 0.69 to 0.94) but did not differ significantly in studies comparing the same beta lactam (Analysis 1.6).

In an analysis restricted to the studies assessing Gram-positive infection, no difference in microbiological failure rates was reported (Analysis 2.13),

Length of hospital stay

Eleven studies published data for the comparison of hospital stay. Significant heterogeneity precluded their combination. Duration of hospitalization was longer with monotherapy in three studies (McCormick 1997; Figueroa-Damian 1996; McCormick 1997; 331 participants), shorter in four studies (Arich 1987; Biglino 1991; Damas 2006; Sexton 1998; 186 participants) and similar in four studies (García Ramírez 1999; Mouton 1990; Wing 1998; Yellin 1993; 540 participants).

Development of resistance and adverse events

We merged studies comparing same and different beta lactams for assessment of development of resistance and adverse events. These outcomes are intended to assess the antibiotic class effect of aminoglycoside-beta lactam combinations versus beta lactams alone, whether same or different.

Bacterial superinfections occurred more frequently with combination therapy (RR 0.75, 95% CI 0.57 to 0.99, 28 studies, 3135 participants; Analysis 1.7). We detected no significant difference in the rates of fungal superinfection (Analysis 1.8). Bacterial colonization was non-significantly more common with combination therapy in all studies reporting on colonization (Analysis 1.9) and in studies in which surveillance cultures were performed routinely (Analysis 1.10). Few studies monitored development of resistance among pathogens isolated initially (Analysis 1.11). We observed no significant difference between monotherapy and combination therapy.

Any adverse event occurred non-significantly more frequently with combination therapy (RR 0.92, 95% CI 0.83 to 1.01; Analysis 1.12), and this analysis was slightly heterogeneous. No significant difference was reported with regard to adverse events requiring treatment discontinuation, but these were reported in a minority of studies (Analysis 1.13). We found nephrotoxicity to be more common in the combination arm in nearly all studies, with a highly significant combined risk ratio in favour of monotherapy (RR 0.30, 95% CI 0.23 to 0.39 Analysis 1.14). A significantly increased rate of nephrotoxicity was seen in studies administering the aminoglycoside once daily and in studies with a multiple-day regimen. Vestibular symptoms and ototoxicity, other known serious side effects of aminoglycoside treatment, were not reported routinely and could not be analysed. Different definitions and detailing of specific adverse events precluded a meaningful meta-analysis of other adverse events, individually or grouped.

DISCUSSION

Summary of main results

The present review compares beta lactam-aminoglycoside antibiotic combinations versus beta lactam monotherapy among non-neutropenic participants with sepsis. The primary outcome that we assessed was all-cause mortality. Twenty-two of the 69 included studies used the same beta lactam in both study arms. Most studies compared one beta lactam versus a different, narrower-spectrum beta lactam combined with an aminoglycoside. Special emphasis should be placed on studies comparing the

same beta lactam. These studies directly test the hypothesis that the addition of an aminoglycoside to the beta lactam is beneficial. Among these studies, all-cause mortality did not differ between study arms (RR 0.97, 95% CI 0.73 to 1.30). Treatment failure occurred more frequently in the monotherapy arm, reaching statistical significance only among the group of 'sepsis' studies. In studies comparing different beta lactams, both failure and mortality were more common in the combination treatment arm. Failure was highly significant, and mortality reached significance only with subgroup analyses. These studies demonstrate an advantage of broad-spectrum beta lactam monotherapy when compared with a narrower-spectrum beta lactam combined with an aminoglycoside, despite equal in vitro coverage of the culprit pathogens in both arms.

Development of resistance was assessed by the occurrence of superinfection and colonization, assuming that bacteria appearing under antibiotic treatment are resistant to the antibiotic administered. Bacterial superinfection occurred significantly more frequently with combination therapy (RR 0.75, 95% CI 0.57 to 0.99). Adverse events occurred more frequently with combination therapy. Specifically, nephrotoxicity occurred significantly more frequently in the combination treatment arm (RR 0.30, 95% CI 0.23 to 0.39). The major adverse event associated with combination therapy was nephrotoxicity. During the past decade, once-daily administration of aminoglycosides has come into use, with similar efficacy but lower nephrotoxicity (Barza 1996). Most studies in our review used multiple-day administration schedules for the complete duration of antibiotic therapy or until modification. The RR of 0.30 for any nephrotoxicity that we observed may, therefore, be an overestimation. However, the RR among the few studies that did administer the aminoglycoside once daily was also highly significant in favour of monotherapy (RR 0.17, 95% CI 0.06 to 0.53).

A small subset of studies in our review addressed participants with Gram-positive infection, mainly *S aureus* endocarditis. No study assessed enterococcal infection specifically. In these, also, no outcome was improved by the addition of an aminoglycoside.

Overall completeness and applicability of evidence

We defined all-cause mortality as the primary outcome, and most studies assessed and reported treatment failure as a main outcome. Obviously, the most significant outcome for the patient is survival following the infectious episode, and this is the ultimate goal in the treatment of sepsis. Available evidence shows that the addition of an aminoglycoside to a beta lactam does not reduce mortality. Replacing beta lactam monotherapy with a narrower-spectrum beta lactam combined with an aminoglycoside may be associated with increased mortality. Failure was commonly defined as lack of clinical improvement, deterioration, relapse and/or modifications to the antibiotic treatment. These endpoints are highly subjective and do not necessarily translate to detriments experienced by the patient. Detection bias is a concern in open trials that compared the same beta lactam and in trials comparing a 'new' broad-spectrum monotherapy versus a conventional antibiotic regimen. Thus, the advantage of monotherapy in studies comparing different beta lactams, and the opposing advantage of combination therapy in studies comparing the same beta lactam, may be largely biased. Failure was poorly correlated with mortality, despite the fact that the clinical failure definition most commonly included infection-related deaths. In 42 trials reporting both deaths and failures, the

Pearson correlation coefficient was 0.36 (RR of 1.0 was assumed for studies with no events in both groups).

The rationale for administering combination therapy arose from in vitro studies showing synergistic bactericidal activity of specific beta lactam-aminoglycoside antibiotic combinations. Synergy has been observed for *P aeruginosa* (Giamarellou 1984), other Gram-negative bacteria (Giamarellou 1986; Klastersky 1976) and staphylococci (Sande 1975; Sande 1976). Assessment of antibiotic efficacy against specific infections in randomized trials must be limited to definitive treatment (randomization performed when infection is microbiologically documented) or must be performed as a subgroup analysis to assess empirical treatment (randomly assigning participants empirically and assessing those with documented infection). Eight studies assessed definitive treatment (semi-empirical studies), and most assessed empirical treatment. We did not find an advantage of combination therapy among participants with any Gram-negative infection, Gram-negative bacteraemia or *P aeruginosa* infection. Lack of data precluded the assessment of *P aeruginosa* bacteraemia. Why does synergy, observed in vitro, not translate into clinical benefit? Specific growth conditions in vitro, unattainable in vivo, may induce synergism. Pharmacokinetic and pharmacodynamic properties involving specific antibiotics, sites of infection, timing and intervals of administration may prevent synergism in vivo. Adverse events related directly to the aminoglycoside, or to the combination, may interfere with an in vivo benefit, amounting altogether to no benefit.

Combination therapy in endocarditis similarly relies on in vitro and in vivo data. Animal studies have shown that sterilization of cardiac vegetations may be achieved more rapidly with combination therapy (Sande 1975; Sande 1976). One clinical study included in our review showed that combination therapy shortened the duration of bacteraemia, but this comparison was performed according to the empirical antibiotic regimen, while randomization occurred empirically or semi-empirically (Korzeniowski 1982). We could not show an advantage of combination therapy by combining all trials in humans. On the contrary, all outcomes tended to favour monotherapy, although statistical significance was not reached.

Quality of the evidence

See [Summary of findings for the main comparison](#).

Among studies comparing the same beta lactam, the quality of evidence of mortality was graded as low, mainly because of imprecision. The 95% confidence intervals range from 27% improved survival to 30% higher risk of death with monotherapy. The quality of evidence for failure was graded as very low because of the indirectness of the outcome and the risk of detection bias associated with assessment of a subjective outcome in open trials (Wood 2008).

In studies using different beta lactams, the quality of evidence for mortality was low because the advantage of monotherapy was derived from studies at unclear risk of bias in relation to allocation concealment and due to suspected publication or reporting bias. The advantage of monotherapy with regard to treatment failure was graded as very low quality of evidence, again because of the indirectness of the failure outcome and the high risk of bias in non-blinded trials.

Potential biases in the review process

A major limitation of existing studies and thus of the compiled analysis is the lack of data for all-cause mortality from more than a third of included studies. This was probably not due to selective reporting bias in that all-cause mortality was not defined as an outcome in included studies. However, the funnel plot for mortality was asymmetrical. Data for subgroups most likely to benefit from combination therapy were also not available from all studies. In our analysis, we did not correct for the appropriateness of antibiotic treatment, which has been shown conclusively to correlate with survival (Ibrahim 2000; Leibovici 1998). Data were not fully available to perform such an analysis. However, among studies comparing the same beta lactam, combination therapy by definition broadened the spectrum of coverage without improving outcomes. In studies comparing different beta lactams, an inappropriate beta lactam was used more frequently in the combination arm, which may partially explain the advantage of monotherapy.

Agreements and disagreements with other studies or reviews

Observational studies tend to show an advantage of combination therapy for severe infection caused by Gram-negative bacteria or *P aeruginosa*. Combination therapy was claimed to be superior to monotherapy in a prospective observational study of participants with *P aeruginosa* bacteraemia, but most participants in the monotherapy group received an aminoglycoside (Hilf 1989). Kumar et al. conducted a large multi-centre retrospective study, including 4662 critically ill participants in the intensive care unit (ICU) with culture-positive, bacterial septic shock. In a propensity-matched analysis (1223 propensity-matched pairs), combination therapy was associated with lower mortality than monotherapy, with an overall hazard ratio for 28-day all-cause mortality of 0.77 (95% CI 0.67 to 0.88; Kumar 2010b). This included all infections (Gram-negative and Gram-positive), and any antibiotics of any class could be included in the combination and monotherapy arms. An analysis restricted to beta lactam-aminoglycosides as combination therapy showed an advantage of combination therapy, but an analysis of beta lactam-aminoglycoside versus beta lactam alone (same or different) is not presented. Bliziotis et al. compared combination therapy versus monotherapy for *P aeruginosa* bacteraemia in a retrospective cohort study and found no significant difference between the regimens, although both mortality and treatment failure were more common with monotherapy (Bliziotis 2011). In contrast, in a prospective study of bacteraemic participants with Gram-negative bacteraemia, we found no significant difference with regard to in-hospital mortality between appropriate beta lactam monotherapy and appropriate beta lactam aminoglycoside combination therapy, both empirically and semi-empirically. Appropriate single aminoglycoside monotherapy was associated with increased mortality (Leibovici 1997). Participants included in observational studies are different from those included in randomized trials. It is possible that an effect that was not observed in randomized controlled trials exists. However, observational studies to date do not provide clear enough conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

We conclude that the addition of an aminoglycoside to a beta lactam does not improve the clinical efficacy achieved with the beta lactam alone. Substituting a narrow-spectrum beta lactam with an aminoglycoside for a single broad-spectrum beta lactam will result in increased failure rates and may be associated with increased mortality. Adverse events occur more frequently with combination treatment. Short-term combination therapy for sepsis does not prevent the development of resistant bacteria, as assessed by superinfection or colonization rates following antibiotic treatment. Thus, the use of beta lactam-aminoglycoside combination therapy for sepsis should be discouraged.

Clinicians usually face the dilemma of selecting an antibiotic treatment on two occasions during an uncomplicated infectious episode. On the initial encounter with a patient, the clinician must prescribe empirical antibiotic treatment because the causative pathogen and its susceptibilities are generally unknown. Most studies addressed this situation, and the results show no difference in overall mortality whether monotherapy or combination therapy is used. Adverse effects, most significantly nephrotoxicity, will occur more frequently with combination therapy. If the choice is between a narrower-spectrum beta lactam combined with an aminoglycoside versus a broad-spectrum beta lactam, our results show that treatment will ultimately have to be modified more frequently if the combination is chosen. We have not identified a specific site of infection or level of disease severity for which combination treatment provides an advantage.

The second decision point occurs when the causative pathogen is identified. Here, the choice of antibiotic treatment is dictated by known susceptibility results. However, the question remains whether for specific bacteria, beta lactam-aminoglycoside combination treatment offers an advantage over single beta lactam treatment. We addressed this question through subgroup analyses of participants with documented infection caused by specific pathogens (Gram-negative pathogens, *P aeruginosa*, *S aureus*). In addition, several semi-empirical studies addressed this question specifically. We have not identified a specific pathogen, or pathogen group, for which combination therapy is advantageous. However, data for these subgroups are very limited.

Overall, appropriate beta lactam monotherapy should be used. Beta lactam-aminoglycoside combination therapy does not offer an advantage and is associated with an increased rate of adverse events.

Implications for research

Innovative trial designs are needed to allow the assessment of participants with severe Gram-negative infection and *P aeruginosa* bacteraemia (Paul 2009). Similarly, the question is still open for endocarditis caused by Gram-positive bacteria, including mainly *S aureus* and *Enterococcus* sp. (Leibovici 2010). The pragmatic randomized trial design using electronic health records might serve as a solution for identification and recruitment of a necessary sample size in multi-centred trials (Staa 2012).

Future trials should differentiate between empirical and definitive antibiotic treatment. Appropriate antibiotic treatment has been shown to significantly reduce mortality and should therefore be

reported, with results adjusted. Outcomes relevant to patients, such as survival and duration of hospitalization, should be assessed. Survival, if not assessed as a primary outcome, must at least be reported as a safety measure in all clinical trials.

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Ishay Silbiger participated in the first version of this review: applied inclusion and exclusion criteria and performed risk of bias assessment, data extraction and analysis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abrams 1979

Methods	RCT Empirical and semi-empirical Gram positive infections
Participants	36 IV drug users with suspected Staphylococcal endocarditis were included. Only those with Staphylococcus aureus bacteraemia and endocarditis according to inclusion criteria were evaluated Patients excluded because they did not fulfil inclusion criteria for bacteraemia were not considered as dropouts for the review
Interventions	Oxacillin 12gr/d vs. oxacillin 12gr/d + gentamicin 80mgX3 (gentamicin administered for the first 2 weeks of a 4-week treatment protocol)
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Adverse events Duration of fever
Notes	USA Outcomes in subgroups: Bacteraemia. Cephalothin was permitted instead of oxacillin for patients with penicillin allergy, and oxacillin was replaced by penicillin for penicillin-susceptible Staphylococcus aureus.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	High risk	Number of randomized patients is unclear
Incomplete outcome data (attrition bias)	High risk	Number of randomized patients is unclear

Abrams 1979 (Continued)

Failure

Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Aguilar 1992

Methods	RCT Sepsis
Participants	36 patients > 16 yrs. with severe infections
Interventions	Ceftizoxime 60-150 mg/kg/d vs. penicillin 20-30mU/d + gentamicin 3-5mg/kg/d
Outcomes	Treatment failure (clinical and bacteriological)
Notes	Mexico No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All 36 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Alvarez-Lerma 2001a

Methods	RCT Sepsis
Participants	140 adult patients hospitalized in the ICU, mechanically ventilated and diagnosed with pneumonia. All infections were hospital acquired. 66% of patients were on inotropic drugs upon entry to study
Interventions	Meropenem 1grX3 for 9.3 days vs. ceftazidime 2grX3 + amikacin 7.5mg/kgX2 for 8.3 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Bacterial superinfections Adverse events Duration of treatment
Notes	Multicentre Spain Outcomes in subgroups: Gram negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated in blocks of 6
Allocation concealment (selection bias)	Low risk	Central randomization and by sealed opaque envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All 140 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	116 out of 140 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Arich 1987

Methods	RCT Partially semi-empirical Sepsis
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Arich 1987 (Continued)

Participants	Adult patients with enterobacteriaceae bacteraemia (at least 2 positive blood cultures with same pathogen). Patients could enter the trial before or at diagnosis of bacteraemia
Interventions	Cefotaxime 1grX3-4 for 17.5 days vs. cefazolin 1grX3 + tobramycin 1.5mg/kgX3 for 10 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfection Adverse events Duration of hospitalizations, treatment and fever
Notes	France (French) Outcomes in subgroups: Bacteraemia Gram-negative infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Sealed opaque numbered envelopes
Incomplete outcome data (attrition bias) Mortality	High risk	47 out of 65 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	47 out of 65 patients randomized were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Banasal 2006

Methods	RCT Community acquired pneumonia
Participants	Children aged 2-59 months with severe or very severe pneumonia with hypoxaemia (SpO2 <90%)

Banasal 2006 (Continued)

Interventions	sequential IV and oral amoxicillin-clavulanate Vs. IV c penicillin 50,000 IU/kg q6h +IV gentamicin 2.5 mg/kg q8h for at least 3 days
Outcomes	Treatment failure (clinical) Duration of treatment
Notes	Chandigarh, India No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization generation
Allocation concealment (selection bias)	Low risk	Labeled sealed envelopes
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All randomized (71) patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Bergeron 1988

Methods	RCT Abdominal
Participants	77 adult patients with severe biliary tract infections (cholecystitis, cholangitis and necrotizing cholecystitis)
Interventions	Cefoperazone 2grX2 for 7.2 days vs. ampicillin 1grX4 + tobramycin 1.5mg/kgX3 following loading dose 2mg/kg for 6.8 days (Surgery in addition to medical treatment was performed in 28/36 monotherapy patients and in 19/29 combination patients, not counted as failure)
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfections Colonization Treatment duration

Bergeron 1988 (Continued)

	Dropouts Adverse events	
Notes	Multicentre Canada Outcomes in subgroups: Bacteraemia	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	High risk	67 out of 77 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	67 out of 77 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Biglino 1991

Methods	RCT Sepsis
Participants	22 patients with severe infections. Patients were compromised by background diseases, including some immune-compromise in 73%. Randomized to 4 arms monotherapy vs. combination, and high vs. low dose of imipenem
Interventions	Imipenem 0.5-1grX4 vs. imipenem 0.5-1grX4 + netilmicin 5mg/kg
Outcomes	Treatment failure (clinical) Adverse events Duration of fever and hospital stay
Notes	Italy No outcomes in subgroups

Biglino 1991 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All randomized (22) patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Brown 1984

Methods	RCT Sepsis
Participants	48 adult patients (34 evaluated) with hospital acquired pneumonia of a documented Gram-negative origin (By sputum's Gram stain or cultures). 85% (29/34) acquired infection in the ICU
Interventions	Moxalactam 2grX3 for 10.1 days vs. carbenicillin 66mg/kgX6 + tobramycin 1.7mg/kgX3 (following a 2-2.5mg/kg loading dose) for 10.6 days
Outcomes	Overall mortality Treatment failure (x-ray non-clearing) Superinfections Adverse events Duration of treatment
Notes	USA Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections 4 deaths among 11 excluded patients not included in outcome assessment

Risk of bias

Bias	Authors' judgement	Support for judgement
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Brown 1984 (Continued)

Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	High risk	34 out of 48 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	34 out of 48 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For failure the assessors were blinded

Carbon 1987

Methods	RCT Probably semi-empirical Sepsis
Participants	47 patients with bacteraemia due to enterobacteriaceae, with at least 3 positive blood cultures entered the study
Interventions	Cefotaxime 1grX4 for 12.9 days vs. cefotaxime 1grX4 + amikacin 7.5mg/kg loading dose followed by a renal-function adjusted maintenance dose for 13.2 days
Outcomes	Overall mortality Treatment failure (clinical) Superinfections Adverse events Duration of treatment and fever
Notes	Multicentre France Outcomes in subgroups: Gram negative infections Bacteraemia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Carbon 1987 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (47) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (47) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Cardozo 2001

Methods	RCT Abdominal
Participants	110 children <15 years, with acute appendicitis
Interventions	Amoxycillin-sulbactam 33mg/kgX3 vs. amoxacillin-sulbactam 33mg/kgX3 + gentamicin 5mg/kgX1
Outcomes	Overall mortality Treatment failure
Notes	Paraguay (Spanish) No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (110) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (110) randomized patients were evaluated for failure outcome

Cardozo 2001 (Continued)

Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Cometta 1994

Methods	RCT Sepsis
Participants	313 adult patients with nosocomial pneumonia, nosocomial sepsis or severe diffuse peritonitis. 73% were in ICU and 48% on mechanical ventilation
Interventions	Imipenem 500mgX4 for 10.2 days vs. imipenem 500mgX4 + netilmicin 150mgX2 for 10.5 days
Outcomes	Overall mortality Treatment failure (clinical) Superinfections Colonization Adverse events Duration of treatment
Notes	Multicentre Switzerland Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections A secondary reference, Iten 1992, described 71 patients from this study, for whom surveillance cultures were performed, and detailed data concerning resistance development are given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Sealed, opaque numbered envelopes
Incomplete outcome data (attrition bias) Mortality	High risk	292 out of 313 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	292 out of 313 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment

Cometta 1994 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Cone 1985

Methods	RCT Sepsis
Participants	57 hospitalized patients with pneumonia or bacteraemia. Pneumonia was community acquired or nosocomial. Only patients with positive bacteriological cultures were evaluated
Interventions	Ceftazidime 2grX3 vs. ticarcillin 3grX4 + tobramycin 1mg/kgX3
Outcomes	Overall mortality Treatment failure (clinical) Superinfections Adverse events
Notes	USA Outcomes in subgroups: Bacteraemia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	High risk	40 out of 57 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	40 out of 57 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Coppens 1983

Methods	RCT Semi-empirical Gram positive infections
Participants	80 patients in whom staphylococcal infections were clinically and microbiologically suspected. Inclusion criteria mandated a positive Gram stain showing Staphylococci Patients were randomized to the designated interventions. 24-48 hours following randomization, patients with documented methicillin-resistant Staphylococci were switched to vancomycin, only in the monotherapy group (N=14). These were excluded from analysis in the review
Interventions	Cefamandole 2grX3 vs. cefamandole 2grX3 + tobramycin 80mgX3
Outcomes	Treatment failure (clinical and bacteriological) Bacterial superinfection and colonization
Notes	Belgium Outcomes in subgroups: Bacteraemia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization generation, Consecutively numbered envelopes
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes, opaque not mentioned
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	66 out of 80 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

D'Antonio 1992

Methods	RCT Sepsis
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D'Antonio 1992 (Continued)

Participants	Non-neutropenic adult patients with altered immune defence, with fever > 38 lasting > 8 hours. 88% of patients with underlying haematological malignancy
Interventions	Ceftriaxone 2grX1 for a median of 12 days vs. ceftriaxone 2grX1 + amikacin 5mg/kgX3 for a median of 11 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfection and colonization (bacterial and fungal) Adverse events Treatment duration
Notes	Italy Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections Bacteraemia Urinary tract infection

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers, stratified according to underlying malignancy
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All (300) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	286 out of 300 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Damas 2006

Methods	RCT Sepsis, ventilator associated pneumonia
Participants	50 adult patients who were mechanically ventilated for more than 48 hours and developed clinical evidence of VAP

Damas 2006 (Continued)

Interventions	IV Cefepime 2 g every 8 hours, for 8-10d Vs. IV Cefepime 2 g every 8 hours+ IV AMIKACIN 20 mg/kg, once daily for 5d
Outcomes	Overall mortality Treatment failure (bacteriological) Superinfection Hospitalisation duration
Notes	Belgium No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (50) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Unclear risk	All (50) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Duff 1982

Methods	Quasi-randomized Abdominal
Participants	74 patients included who developed endomyo-parametritis after caesarian section or vaginal delivery, or who developed pelvic cellulitis after hysterectomy
Interventions	Cefoxitin 2grX3 vs. penicillin 5millUX4 + gentamicin 60-80mgX3
Outcomes	Overall mortality Treatment failure Adverse events

Duff 1982 (Continued)

Dropouts

Notes
USA
Outcomes in subgroups: Gram-negative infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Inadequate randomization generation - Based on the last digit of hospitalization number, odds/evens
Allocation concealment (selection bias)	High risk	Inadequate randomization concealment
Incomplete outcome data (attrition bias) Mortality	Low risk	All (74) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Unclear risk	All (74) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Dupont 2000

Methods	RCT Abdominal
Participants	241 patients evaluated with severe generalized peritonitis.
Interventions	Piperacillin- tazobactam 4grX4 for 8.2 days vs. piperacillin- tazobactam 4grX4 + amikacin 7.5mg/kgX2 for 8.6 days. In addition all patients were operated on
Outcomes	Overall mortality Treatment failure (clinical) Adverse events Dropouts Treatment duration
Notes	Multicentre France No outcomes in subgroups

Risk of bias

Dupont 2000 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated in blocks of 4 patients
Allocation concealment (selection bias)	Low risk	Central randomization
Incomplete outcome data (attrition bias) Mortality	Unclear risk	227 out of 241 randomized patients were evaluated for failure outcome
Incomplete outcome data (attrition bias) Failure	Unclear risk	204 out of 241 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only outcome assessor blinded

Felisart 1985

Methods	RCT Sepsis
Participants	73 adult patients with underlying advanced cirrhosis, presenting with severe bacterial infections. Most patients had spontaneous bacterial peritonitis
Interventions	Cefotaxime 2grX6 vs. ampicillin 2grX6 + tobramycin renal adjusted maintenance dose X3/d following 1.75mg/kg loading dose
Outcomes	Overall mortality Treatment failure (clinical) Superinfections Adverse events
Notes	Spain Outcomes in subgroups: Bacteraemia Urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers

Felisart 1985 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	All (73) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Unclear risk	All (73) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Figuerola-Damian 1996

Methods	RCT Abdominal, post cesarean endometritis
Participants	56 adult patients with post cesarean endometritis.
Interventions	IV piperacillin/tazobactam 500MG x 4/D for 5 days Vs. IV ampicillin 1gr X 4/d + IV Gentamicin 80mg X 3/d, for 4 days;
Outcomes	Treatment failure (clinical) Adverse events Duration of fever and hospitalization
Notes	Mexico No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported, Randomization ratio 1:3
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported

Figueroa-Damian 1996 (Continued)

Incomplete outcome data (attrition bias) Failure	Low risk	All (56) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Finer 1992

Methods	RCT Sepsis
Participants	471 adult patients hospitalized with signs and symptoms of serious bacterial infections, thought by the physician to require parenteral antibiotic treatment
Interventions	Ceftazidime 2grX2 vs. ureidopenillin + aminoglycoside used routinely in specific Center: piperacillin-gentamicin (73p); ampicillin-gentamicin (69p); mezlocillin-netilmicin (44p); piperacillin-netilmicin (20p)
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfections Colonization Drop-outs after randomization Adverse events
Notes	Multicentre UK Outcomes in subgroups: Bacteraemia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Incomplete outcome data (attrition bias) Mortality	High risk	All (471) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias)	High risk	415 out of 471 randomized patients were evaluated for failure outcome

Finer 1992 (Continued)

Failure

Other bias	Unclear risk	Fixed time for outcome assessment (within 72 hours of stopping the treatment)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

García Ramírez 1999

Methods	RCT Sepsis, Nosocomial pneumonia
Participants	60 adult patients with Nosocomial pneumonia, divided to 2 groups.
Interventions	IV Ceftazidime Vs. IV penicillin + amikacin
Outcomes	Treatment failure (clinical) Duration of hospitalization
Notes	Tacuba Outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	According to patient descriptives, groups very different at baseline. Randomization methods not given
Allocation concealment (selection bias)	High risk	According to patient descriptives, groups very different at baseline. Randomization methods not given
Incomplete outcome data (attrition bias) Mortality	Low risk	All (60) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (60) randomized patients were evaluated for mortality outcome
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias)	High risk	Open

García Ramírez 1999 (Continued)

All outcomes

Gerecht 1989

Methods	RCT Abdominal
Participants	82 patients with suspected cholangitis were randomized empirically. Only those with bacteraemia or positive bile cultures, and fulfilling clinical criteria for cholangitis were evaluated. Patients who were not evaluated because they did not meet inclusion criteria are not considered as dropouts for the review
Interventions	Mezlocillin 4grX4 for 11.9 days vs. ampicillin 1grX4 + gentamicin 1.5mg/kgX3 for 10.3 days. In addition to antibiotic therapy all patients underwent surgical intervention
Outcomes	Treatment failure (clinical and bacteriological) Superinfections Adverse events Duration of treatment
Notes	USA No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by computer generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	Only infection related mortality was reported
Incomplete outcome data (attrition bias) Failure	Low risk	415 out of 82 randomized patients were evaluated for failure outcome (36 were not evaluated - 32 did not fulfil the study inclusion criteria for evaluation, 3 did not adhere to the protocol and 1 excluded because of resistant infection)
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Gomez 1990a

Methods	RCT Sepsis
Participants	197 patients with suspected Gram-negative bacteraemia randomized. Patients with proven Gram-negative bacteraemia (78) were analysed. Patients who were not evaluated because they did not meet inclusion criteria for bacteraemia were not considered as dropouts
Interventions	Ceftazidime 1grX4 for 10 days vs. cefradine 1grX6 + amikacin 7.5mg/kgX2 for 10 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfection (bacterial and fungal) Adverse events Duration of treatment
Notes	Spain (Spanish) Outcomes in subgroups: Bacteremia Gram-negative infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by computer generated table of random numbers
Allocation concealment (selection bias)	Low risk	Sealed opaque closed envelopes
Incomplete outcome data (attrition bias) Mortality	High risk	78 out of 197 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	78 out of 197 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Hasali 2005

Methods	RCT single blind Sepsis, Community-acquired pneumonia
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Hasali 2005 (Continued)

Participants	Pediatric patients (aged 2m to 5 years) diagnosed with Community-acquired pneumonia
Interventions	IV ampicillin 100 mg/kg/day divided every 6 h Vs. IV ampicillin 100 mg/kg/day divided every 6 h + IV Gentamicin 5mg/kg x 1/d
Outcomes	Duration of treatment, fever and hospitalization
Notes	Malaysia No outcome in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	consecutive, fixed sample of 20 per group
Allocation concealment (selection bias)	High risk	consecutive, fixed sample of 20 per group
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	Unclear risk	No failure outcome reported
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	open (stated as single blind but no blinding described)
Blinding of outcome assessment (detection bias) All outcomes	High risk	open (stated as single blind but no blinding described)

Havig 1973

Methods	RCT Abdominal
Participants	68 adult patients evaluated with acute cholecystitis verified histologically or by roengten. Trial included 3 arms, of which 2 are included in the review
Interventions	IM ampicillin 0.5grX4 vs. IM chloramphenicol 1grX2 (arm not included in review) vs. IM benzyl-penicillin 400,000IEX2 + IM streptomycin 0.5grX2. In addition 10/24 patients in the ampicillin arm and 15/26 patients in the combination arm were operated on
Outcomes	Overall mortality Treatment failure (clinical)

Havig 1973 (Continued)

Duration of fever

Notes
Norway
No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization list prepared in advanced
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	High risk	50 out of 90 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	68 out of 90 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Hoepelman 1988

Methods	RCT Sepsis
Participants	105 patients with serious bacterial infections were included. Of these 18% were neutropenic and are not included for the analysis in this review
Interventions	Ceftriaxone 2grX1 vs. cefuroxime 1.5grX3 + gentamicin 80mgX3 (following by an initial 1.5mg/kg dose)
Outcomes	Overall mortality Treatment failure (clinical) Superinfections Fungal colonization Adverse events
Notes	Netherlands Outcomes for subgroups were not extracted, as they are given in the publication for the whole group including neutropenic patients Outcomes for non-neutropenic patients were obtained from the author

Risk of bias

Bias	Authors' judgement	Support for judgement
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Hoepelman 1988 (Continued)

Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Low risk	Adequate randomization concealment by sealed opaque envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All (86) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (86) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Holloway 1985

Methods	RCT Sepsis Semi-empirical
Participants	43 adult patients with suspected Gram-negative septicaemia, or pneumonia, randomized when blood cultures were positive for a Gram-negative pathogen
Interventions	Ticarcillin-clavulanic acid 3.1grX4-6 vs. piperacillin 50mg/kgX4-6 + tobramycin 1-1.5mg/kgX3-4
Outcomes	Treatment failure (clinical and bacteriological) Adverse events
Notes	USA Outcomes in subgroups: Bacteremia Gram-negative infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	No mortality outcome reported

Holloway 1985 (Continued)

Mortality

Incomplete outcome data (attrition bias) Failure	High risk	33 out of 43 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Iakovlev 1998

Methods	RCT Sepsis
Participants	95 adult patients with severe nosocomial infections
Interventions	Meropenem 1grX3 for 9 days vs. ceftazidime 1grX3 + amikacin 500mgX2 for 9 days
Outcomes	Treatment failure (clinical and bacteriological) Duration of treatment Adverse events
Notes	Multicentre Russia (Russian) Outcomes in subgroups: Urinary tract and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	By sealed envelopes, opaque not mentioned
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	Low risk	All (95) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment

Iakovlev 1998 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Jaspers 1998

Methods	RCT Sepsis
Participants	79 elderly patients (> 65yrs.) with sepsis syndrome and suspected bacteraemia, pneumonia, intra-abdominal sepsis, or complicated urinary tract infection
Interventions	Meropenem 1grX3 for 7.5 days vs. cefuroxime 1.5grX3 + gentamicin 4mg/kgX1 for 7.4 days (metronidazole 500mgX4 added to patients receiving combination in case of abdominal sepsis (15 patients overall))
Outcomes	Overall mortality Treatment failure (clinical and microbiological) Bacterial superinfections Adverse events Duration of treatment
Notes	Multicentre Netherlands Outcomes in subgroups: Urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers in consecutive envelopes
Allocation concealment (selection bias)	Low risk	Randomization by consecutive sealed, opaque envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All (79) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (79) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment (end of treatment)
Blinding of participants and personnel (performance bias)	High risk	Open

Jaspers 1998 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
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Klustersky 1973

Methods	RCT Sepsis
Participants	75 adult patients with disseminated cancer and life threatening infections, presumed Gram-negative. Randomized to 3 arms, of which 2 are relevant for the review. 18% of patients leukopenic (leukopenia not defined) - no information for neutropenia
Interventions	Carbenicillin 10grX3 for 8.3 days vs. carbenicillin 10grX3 + gentamicin 160mgX3 (IM or IV) for 9 days vs. gentamicin 160mgX3 (3rd arm, not included in review)
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Colonization and Superinfection Duration of treatment Dropouts
Notes	Belgium Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections Bacteremia Urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	High risk	45 out of 50 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	46 out of 50 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open

Klastersky 1973 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
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Kljucar 1990

Methods	RCT Sepsis
Participants	150 patients > 14yrs. hospitalized in the intensive care unit and ventilated, with nosocomially acquired pneumonia. Randomized to 3 arms (2 combination and 1 monotherapy)
Interventions	Ceftazidime 2grX3 vs. ceftazidime 2grX3 + tobramycin 80mgX3 vs. azlocillin 5mgX3 + tobramycin 80mgX3, overall for 6.6 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological)
Notes	Germany No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization
Allocation concealment (selection bias)	Low risk	Adequate randomization concealment by sealed consecutive envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	99 out of 100 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	99 out of 100 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Koehler 1990

Methods	RCT
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Koehler 1990 (Continued)

Sepsis

Participants	144 patients > 18 yrs. with nosocomially acquired pneumonia
Interventions	Ceftazidime 1grX3 vs. piperacillin 4grX3 + tobramycin 80mgX3
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Bacterial and fungal colonization Dropouts
Notes	Multicentre Germany Outcomes in subgroups: Gram negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (144) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	127 out of 144 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Korzeniowski 1982

Methods	RCT Partially semi-empirical Gram positive infections
Participants	156 patients with clinically suspected infective endocarditis were randomized (prior antibiotic treatment of < 48 hours permitted) 78 patients with Staphylococcus aureus bacteraemia and endocarditis were analysed: 48 drug addicts and 30 non-addicts (14 patients randomized semi-empirically)

Korzeniowski 1982 (Continued)

Interventions	Nafcillin 1.5-6grX6 vs. nafcillin 1.5-6grX6 + gentamicin 1mg/kgX3 administered for the first 2 weeks of a 4-week treatment protocol
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Dropouts Need for surgery Adverse events Duration of bacteraemia and fever are other outcomes shown in the study, but these are shown by groups of empirical treatment regimen which was not always randomly allocated
Notes	Multicentre USA Outcomes in subgroups: Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization by table of random number
Allocation concealment (selection bias)	Low risk	Adequate randomization concealment, central randomization
Incomplete outcome data (attrition bias) Mortality	High risk	74 out of 156 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	74 out of 156 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Landau 1990

Methods	Quasi-randomized Urinary tract infections
Participants	40 adult patients hospitalized with complicated urinary tract infection
Interventions	Ceftriaxone 2grX1 vs. cefazolin 1grX3 + gentamicin 80mgX3
Outcomes	Overall mortality

Landau 1990 (Continued)

	Treatment failure (bacteriological only) Adverse events Drop-outs after randomization Duration of fever
Notes	Israel (Hebrew) Outcomes in subgroups: Urinary tract and Gram-negative infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization according to last digit of identification number - odds vs. evens
Allocation concealment (selection bias)	High risk	Inadequate randomization concealment
Incomplete outcome data (attrition bias) Mortality	Low risk	All (40) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (40) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Limson 1988

Methods	RCT Sepsis
Participants	54 adult patients randomized, of which 40 patients with severe Gram-negative infections were evaluated
Interventions	Ceftazidime 2grX2 vs. ticarcillin 3grX3-4 + amikacin 500mgX2 (or 15mg/kgX1)
Outcomes	Treatment failure (clinical and microbiological) Fungal superinfections Adverse events
Notes	The Philippines Outcomes in subgroups: Bacteremia Gram negative, and Pseudomonas sp. infections

Limson 1988 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	40 out of 54 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Mandell 1987

Methods	RCT Sepsis
Participants	110 patients > 16yrs. evaluated with community acquired or nosocomial pneumonia (2/3 nosocomial)
Interventions	Ceftazidime 2grX3 vs. cefazolin 1.5grX3 or ticarcillin 3grX4 + tobramycin 1.7mg/kgX3
Outcomes	Treatment failure (clinical and bacteriological) Superinfections Colonization (including resistant development) Adverse events
Notes	Multicentre Canada Outcomes in subgroups: Bacteraemia Gram-negative infections. Cefazolin replaced by ticarcillin for combination group patients with documented Pseudomonas infections

Risk of bias

Bias	Authors' judgement	Support for judgement
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Mandell 1987 (Continued)

Random sequence generation (selection bias)	Low risk	Generated by coin tosses
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes opened in numerical order, opaque not mentioned
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	110 out of 129 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Martin 1991

Methods	RCT Urinary tract infections
Participants	116 patients hospitalized with suspected pyelonephritis
Interventions	Ceftriaxone 2grX1 vs. ampicillin 1grX4 + gentamicin 1mg/kgX3
Outcomes	Treatment failure (clinical) Superinfection (relapse and re-infections) Dropouts Adverse events
Notes	Brussels (French) Outcomes in subgroups: Urinary tract infections Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation by randomization table
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	No mortality outcome reported

Martin 1991 (Continued)

Mortality

Incomplete outcome data (attrition bias) Failure	Unclear risk	94 out of 116 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

McCormick 1997

Methods	RCT Sepsis
Participants	128 adult patients with chronic liver disease (cirrhosis) and suspected or proven sepsis
Interventions	Ceftazidime 2grX2 for 5 days vs. mezlocillin 5grX3 + netilmicin 3mg/kgX2 for 4 days
Outcomes	Overall mortality Treatment failure (clinical) Adverse events Duration of treatment and hospital stay
Notes	Ireland Outcomes in subgroups: Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation by randomization table
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Incomplete outcome data (attrition bias) Mortality	High risk	128 out of 147 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	128 out of 147 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment

McCormick 1997 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Mergoni 1987

Methods	RCT Sepsis
Participants	42 adult patients in ICU with severe infections
Interventions	Azlocillin 13+-2.2gr for 6.5 days vs. azlocillin 14.1+-1gr + amikacin 1.16+-0.027gr for 7.2 days (all in for daily doses)
Outcomes	Treatment failure (clinical and bacteriological) Adverse events Duration of treatment
Notes	Italy Outcomes in subgroups: Gram negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes that were provided by the study center
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	Low risk	All (42) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Moreno 1997

Methods	RCT Sepsis
Participants	Renal or (kidney-pancreas) transplant patients with fever and suspected bacterial infection
Interventions	Imipenem-cilastatin 500mgX4 vs. piperacillin 4grX3 + tobramycin 80mgX2
Outcomes	Treatment failure (clinical and bacteriological)
Notes	Spain Outcomes in subgroups: Gram negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	58 out of 70 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Mouton 1990

Methods	RCT Sepsis
Participants	211 adult patients hospitalized in intensive care unit with respiratory tract infections
Interventions	Imipenem 500mgX4 for 11.1 days vs. cefotaxime 1grX4 + amikacin 5mg/kgX3 for 10.4 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological)

Mouton 1990 (Continued)

	Superinfections Colonization Hospitalization duration Duration of treatment
Notes	Multicentre France (French) Outcomes in subgroups: Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (211) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (211) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Mouton 1995

Methods	RCT Sepsis
Participants	237 adult patients with community or hospital acquired serious infections, excluding intra-abdominal sepsis (urinary tract infection included)
Interventions	Meropenem 1grX3 for 8.8 days vs. ceftazidime 2grX3 + amikacin 5-7.5mg/kgX2-3 for 8.3 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfections Adverse events Dropouts Duration of treatment
Notes	Multicentre

Mouton 1995 (Continued)

Europe
Outcomes in subgroups:
Bacteremia
Gram negative and Pseudomonas sp. and urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	No reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (237) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	229 out of 237 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment (end of treatment)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Muller 1987

Methods	RCT Abdominal
Participants	Trial includes 3 arms (2 monotherapies, 1 combination treatment) 106 patients evaluated with acute cholecystitis or cholangitis
Interventions	Piperacillin 3grX6 for 7.4 days vs. cefoperazone 2grX3 for 8.1 days vs. ampicillin 2grX4 + tobramycin 1-1.5mg/kgX3 following 1.5mg/kg loading dose for 11.1 days
Outcomes	Treatment failure (clinical) Adverse events Duration of treatment
Notes	Bi-centre USA No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
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Muller 1987 (Continued)

Random sequence generation (selection bias)	Low risk	The randomization was computer generated for each center
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	106 out of 131 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Naime Libien 1992

Methods	RCT Sepsis
Participants	30 children aged 1m - 11yr with severe lower respiratory tract infections
Interventions	Ceftizoxime 20-50mg/kgX2-3 vs. penicillin 0.7-1.7 megaunit/kgX3 + gentamicin 1-1.5mg/kgX2
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Adverse events Duration of fever
Notes	Mexico (Spanish) No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (30) randomized patients were evaluated for mortality outcome

Naime Libien 1992 (Continued)

Incomplete outcome data (attrition bias) Failure	Low risk	All (30) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Piccart 1984

Methods	RCT Sepsis
Participants	105 adult, non-neutropenic, cancer patients with suspected Gram-negative infections. Study included both neutropenic and non-neutropenic patients, but analysis was completely separated Patients with Gram-positive bacteraemia were excluded
Interventions	Cefoperazone 6grX2 vs. cefoperazone 2grX2 + amikacin 500mgX2
Outcomes	Treatment failure (clinical and bacteriological) Superinfections (bacterial and fungal) Drop-outs after randomization
Notes	Belgium Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	87 out of 105 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment

Piccart 1984 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Rapp 1984

Methods	RCT Sepsis
Participants	35 adult patients hospitalized in a neurosurgical intensive care unit. All with nosocomial pneumonia
Interventions	Ceftazidime 2grX3 vs. ticarcillin 3grX4 + tobramycin pharmacokinetically adjusted doses after 1.75mg/kd loading dose
Outcomes	Treatment failure (clinical and bacteriological) Adverse events
Notes	USA Outcomes in subgroups: Gram negative bacteraemia Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	Low risk	All (35) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Rasmussen 1986

Methods	RCT Urinary tract infections
Participants	62 adult patients hospitalized in a urosurgical department with urinary tract infections, mostly post-operative
Interventions	Cefotaxime 3grX3 for 5.4 days vs. ampicillin 1grX4 + netilmicin 150mgX3 for 7 days
Outcomes	Treatment failure (clinical) Relapse Duration of fever and treatment Adverse events
Notes	Denmark Outcomes in subgroups: Urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes, opaque not mentioned
Incomplete outcome data (attrition bias) Mortality	High risk	59 out of 62 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	59 out of 62 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Ribera 1996

Methods	RCT Semi-empirical Gram-positive infections
Participants	Spain

Ribera 1996 (Continued)

90 intravenous drug users randomized, of which 74 had *Staphylococcus aureus* right-sided endocarditis. 90.5% of patients were HIV positive. Diagnostic criteria for possible (13% of study patients), probable (34%) and definitive endocarditis (53%) are defined in study

Interventions	Cloxacillin 2grX6 vs. cloxacillin 2grX6 + gentamicin 1mg/kgX3
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Relapse, re-infection and need for surgery Duration of treatment Adverse events
Notes	Spain Journal publication. Outcomes in subgroups: Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization generation
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All (90) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (90) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Rubinstein 1995

Methods	RCT Sepsis
Participants	580 adult patients with serious hospital acquired infections and a diagnosis of sepsis, pneumonia or upper urinary tract infection
Interventions	Ceftazidime 2grX2 for 9 days vs. ceftriaxone 2grX1 + tobramycin 3-5mg/kgX1 following 2mg/kg loading dose for 9 days

Rubinstein 1995 (Continued)

Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfections Duration of treatment Adverse events
Notes	Multicentre Europe, Middle East, Asia, South America Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections Bacteremia Urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All (580) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	491 out of 580 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment - 14 days after treatment cessation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded

Sage 1987

Methods	RCT Sepsis
Participants	93 patients > 14yrs. randomized to 3 arms, of which 2 are usable in the review. The 3rd arm is aminoglycoside monotherapy. Patients were suspected of a life threatening sepsis, thought to be caused by Enterobacteriaceae or Staphylococci
Interventions	Cefotaxime 1-2grX4 for 7.4 days vs. cefotaxime 1-2grX4 + netilmicin 2-3mg/kgX3 (3rd arm, not used - netilmicin 2-3mg/kgX3) for 8.7 days
Outcomes	Treatment failure (clinical and bacteriological) Bacterial and fungal superinfections

Sage 1987 (Continued)

	Dropouts Adverse events Duration of treatment
Notes	UK Outcomes in subgroups: Bacteremia Gram negative and urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	No reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	48 out of 61 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Sandberg 1997

Methods	RCT Urinary tract infections
Participants	73 adult female patients with suspected pyelonephritis
Interventions	Cefotaxime 1grX2 for 2 days followed by oral cefadroxil 1grX2 vs. cefotaxime 1grX2 + tobramycin 160mgX1 for 2 days, followed by oral cefadroxil 1 grX2
Outcomes	Treatment failure (clinical and bacteriological) Superinfection and colonization (relapse, re-infections and asymptomatic bacteriuria recurrence) Adverse events Drop-outs after randomization Duration of fever
Notes	Multicentre Sweden

Sandberg 1997 (Continued)

Outcomes in subgroups: Urinary tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated lists in blocks of four were used at each center
Allocation concealment (selection bias)	Low risk	Sealed opaque envelope allocation
Incomplete outcome data (attrition bias) Mortality	Low risk	All (73) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	61 out of 73 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Sanfilippo 1989

Methods	RCT Abdominal
Participants	26 female patients aged 16-19 years with acute pelvic inflammatory disease
Interventions	Mezlocillin 62.5mg/kgX4 vs. penicillin 480,000U/kgX4 + tobramycin 1mg/kgX3
Outcomes	Treatment failure (clinical)
Notes	USA No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated code
Allocation concealment (selection bias)	Low risk	Adequate central randomization

Sanfilippo 1989 (Continued)

Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	Low risk	All (26) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment - 4 weeks after discharge
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment were blinded

Sculier 1982

Methods	RCT Sepsis
Participants	20 adult, intubated, patients with Gram-negative pneumonia in the neurosurgical intensive-care unit Patients were randomized when presenting with radiographic broncho-pneumonia, purulent sputum and Gram-negative rods on sputum direct smear
Interventions	Mezlocillin 10grX3 vs. mezlocillin 10grX3 + sisomicin 75mgX3. In addition to allocated systemic treatment, all patients received intra-tracheal sisomycin 25mgX3/d
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Bacterial colonization Resistance development Adverse events
Notes	Belgium Outcomes in subgroups: Gram negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (20) randomized patients were evaluated for mortality outcome

Sculier 1982 (Continued)

Incomplete outcome data (attrition bias) Failure	Low risk	All (20) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment -1 week after treatment cessation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Sexton 1998

Methods	RCT Semi-empirical Gram-positive infections
Participants	67 adult patients randomized, of which 51 with native valve endocarditis (defined by Duke criteria) caused by penicillin-susceptible Streptococci.
Interventions	Ceftriaxone 2grX1 for 4 weeks vs. ceftriaxone 2grX1 + gentamicin 3mg/kgX1 for 2 weeks
Outcomes	Treatment failure (clinical and bacteriological) Relapse and re-infection Adverse events Dropouts Duration of hospital stay Need for surgery
Notes	Multicentre USA Outcomes in subgroups: Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	51 out of 67 randomized patients were evaluated for failure outcome

Sexton 1998 (Continued)

Other bias	Unclear risk	Fixed time for outcome assessment (3 month)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Sieger 1997

Methods	RCT Sepsis
Participants	211 adults >18yrs. with hospital-acquired lower respiratory tract infections. 70% intubated and 27% with severe pneumonia
Interventions	Meropenem 1grX3 for 7.8 days vs. ceftazidime 2grX3 + tobramycin 1mg/kgX3 (following 1.5-2mg/kg loading dose) for 7.4 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfections Adverse events Duration of treatment
Notes	Multicentre USA Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections. Study performs both efficacy and ITT analysis, with a drop-out rate of 43% for the efficacy analysis. Outcomes were extracted by ITT. Superinfections and subgroup analyses are given only by efficacy analysis in study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (211) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (211) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment (30 days)

Sieger 1997 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Smith 1984

Methods	RCT Sepsis
Participants	200 adult patients randomized with suspected or proven serious infections. 195 who actually received study drugs were evaluated for efficacy
Interventions	Cefotaxime 2grX6 + placebo X3 for 5 days vs. nafcillin 1.5grX6 + tobramycin 2mg/kgX3 for 5.3 days (Addition of clindamycin 600mgX3 to both groups permitted for suspected anaerobic infections)
Outcomes	Overall mortality Treatment failure (clinical and microbiological) Bacterial superinfections Colonization Adverse events Duration of treatment
Notes	USA Outcomes in subgroups: Urinary tract and Gram negative infections. Two additional references refer to the same trial: Moore 1986a (cost-effectiveness analysis), and Moore 1986b (nephrotoxicity analysis). Overall mortality, and treatment duration are taken from Moore 1986a that analysed all patients given study drugs. Cost outcome not included in the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by table of random numbers
Allocation concealment (selection bias)	Low risk	Central randomization. Identically labelled mini bottles containing antibiotic or placebo, with colour added to mask the yellow colour of cefotaxime.
Incomplete outcome data (attrition bias) Mortality	High risk	187 out of 200 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	195 out of 200 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment

Smith 1984 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded

Speich 1998

Methods	RCT Sepsis
Participants	89 adults >16yrs. with severe pneumonia. Community acquired in 89%
Interventions	Piperacillin-tazobactam 4.5grX3 for 10.2 days vs. amoxicillin-clavulonic acid 2.2grX3 + gentamicin or netilmicin 3-6mg/kgX1 for 10.1 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Dropouts Adverse events Duration of treatment
Notes	Multicentre Switzerland No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by computer derived program
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All (89) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	84 out of 89 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias)	High risk	Open

Speich 1998 (Continued)

All outcomes

Stille 1992

Methods	RCT Sepsis
Participants	337 adult patients randomized with non-life-threatening infections, of abdominal, gynaecological or respiratory tract origin (UTI, skin, bone, and CNS infections excluded)
Interventions	Imipenem 500mgX3 for 8.4 days vs. cefotaxime 2grX3 + gentamicin 0.66-1mg/kgX3 for 8.2 days (metronidazole allowed in combination treatment group for suspected anaerobic infection)
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Colonization and resistance development Adverse events Duration of treatment
Notes	Multicentre Germany and Austria Outcomes in subgroups: Gram negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By a computer generated list of blocks of 16 patients
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	All (337) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Unclear risk	All (337) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Sukoh 1994

Methods	RCT Sepsis
Participants	63 patients with respiratory tract infections and underlying respiratory disease
Interventions	Cefoperazone/ sulbactam 1-4gr/d for 11.7 days vs. Cefoperazone/ sulbactam 2-6gr/d + one of several aminoglycosides in low doses (amikacin 100-400 mg/d 16 patients, tobramycin 40-180 mg/d 15 patients, isepamicin 400 mg/d 1 patient, netilmicin 200 mg/d 1 patient) for 11.1 days
Outcomes	Treatment failure (clinical and bacteriological)
Notes	Japan (Japanese) Outcomes in subgroups: Gram-negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Randomized by envelope method
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	Low risk	All (63) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Takamoto 1994

Methods	RCT Sepsis
Participants	171 adult patients with respiratory tract infections
Interventions	Imipenem/cilastatin sodium vs. imipenem/cilastatin sodium + amikacin sulfate
Outcomes	Treatment failure (clinical and bacteriological) Drop-outs after randomization

Takamoto 1994 (Continued)

Adverse events

Notes
Multicentre Japan (Japanese) Outcomes in subgroups:
Gram-negative and Pseudomonas sp. infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By a computer generated code
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	154 out of 171 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Thompson 1990

Methods	RCT Abdominal
Participants	96 patients evaluated with acute cholangitis (cholecystitis not included)
Interventions	Piperacillin 3grX6 for 8.4 days vs. ampicillin 2grX4 + tobramycin 1-1.5mg/kgX3 for 9.1 days (following 1.5mg/kg loading dose). In addition 35/96 patients were operated on
Outcomes	Overall mortality Treatment failure (clinical) Adverse events Treatment duration
Notes	Multicentre USA No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
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Thompson 1990 (Continued)

Random sequence generation (selection bias)	Low risk	By computer generated for each center
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	High risk	96 out of 106 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	96 out of 106 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Thompson 1993

Methods	RCT Abdominal
Participants	120 patients evaluated with acute biliary tract infections (cholecystitis and cholangitis)
Interventions	Cefepime 2grX2 for 7.5 days vs. mezlocillin 3grX6 + gentamicin 1.5mg/kgX3 for 7 days. In addition, 118/120 patients were operated on
Outcomes	Overall mortality Treatment failure (clinical) Adverse events Treatment and hospitalization duration
Notes	Multicenter USA No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By computer generated for each center
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	120 out of 147 randomized patients were evaluated for mortality outcome

Thompson 1993 (Continued)

Mortality

Incomplete outcome data (attrition bias) Failure	High risk	120 out of 147 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Trujillo 1992

Methods	RCT Sepsis
Participants	30 adult patients with severe skin and soft tissue or respiratory tract infections
Interventions	Ceftizoxime 1-2grX3 vs. ampicillin 1-3grX4 + gentamicin 3-5mg/kg/d, overall for 10 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Adverse events Fever duration
Notes	Mexico (Spanish) No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	All (30) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Unclear risk	All (30) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment

Trujillo 1992 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Vernon 1985

Methods	RCT Sepsis
Participants	30 adult patients with severe broncho-pulmonary infections
Interventions	Cefoperazone 2grX2 for 16.8 days vs. ampicillin 1.5grX4 + tobramycin 1mg/kgX3 for 11.8 days
Outcomes	Treatment failure (clinical) Resistant colonization Adverse events Duration of treatment
Notes	France (French) No outcomes in subgroups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization generation
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	Low risk	All (30) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Verzasconi 1995

Methods	RCT Urinary tract infections
Participants	93 adult patients with acute pyelonephritis or complicated urinary tract infections
Interventions	Amoxicillin-clavulonate 2.2grX3 for 4.1 days vs. amoxicillin 2grX3 + gentamicin 1.5mg/kg loading followed by maintenance for 4.2 days
Outcomes	Treatment failure (bacteriological) Superinfection Dropouts Treatment and fever duration Adverse events
Notes	Bi-centre Switzerland (German) Outcomes in subgroups: Urinary tract infection

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	No mortality outcome reported
Incomplete outcome data (attrition bias) Failure	High risk	87 out of 93 randomized patients were evaluated for mortality outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinded

Warren 1983

Methods	RCT Sepsis
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Warren 1983 (Continued)

Participants	120 adult patients with suspected or known life-threatening infections caused by Gram-negative bacilli
Interventions	Cefoperazone 1.5grX4 for a median of 9 days vs. cefamandole 2grX6 + tobramycin 1.7mg/kg loading dose, followed by drug- level-adjusted maintenance dose for a median of 8 days
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Superinfection Duration of treatment Adverse events Drop-outs after randomization
Notes	USA Outcomes in subgroups: Bacteremia Gram-negative infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization generation by random numbers
Allocation concealment (selection bias)	Unclear risk	By sealed envelopes
Incomplete outcome data (attrition bias) Mortality	High risk	120 out of 123 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	120 out of 123 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment (14 days after treatment cessation)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Wiecek 1986

Methods	RCT Urinary tract infections
Participants	20 adult patient with acute pyelonephritis
Interventions	Ceftazidime 1grX3 vs.

Wiecek 1986 (Continued)

cefotaxime 1grX2 + tobramycin 1mg/kgX3

Outcomes	Treatment failure (bacteriological) Re-infection Adverse events
Notes	Poland Outcomes in subgroups: Gram negative and Pseudomonas sp. infections Urinary tract infections Bacteremia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Mortality	Low risk	All (20) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (20) randomized patients were evaluated for bacteriologic failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Wing 1998

Methods	RCT Urinary tract infections
Participants	179 pregnant women <24 weeks gestation with pyelonephritis randomized to 2 monotherapy arms and 1 combination therapy arm
Interventions	Cefazolin 1grX3 vs. ceftriaxone 1grX1 vs. ampicillin 2grX4 + gentamicin 1.75mg/kgX3 (after 2mg/kg loading)
Outcomes	Overall mortality Treatment failure (clinical and bacteriological) Re-infection Fever and hospitalization duration

Wing 1998 (Continued)

Notes	Bi-centre USA Outcomes in subgroups: Urinary tract infections
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number table n
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Incomplete outcome data (attrition bias) Mortality	Low risk	All (179) randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	Low risk	All (179) randomized patients were evaluated for failure outcome
Other bias	Unclear risk	Fixed time for outcome assessment (2 weeks following treatment cessation)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Yellin 1993

Methods	RCT Abdominal
Participants	179 patients with clinically suspected cholecystitis Only those operated on while on allocated treatment were evaluated (infection proven at surgery) Patients who were not evaluated because surgery was not performed or incorrect diagnosis are not considered as drop-outs for the review
Interventions	Cefepime 2grX2 for 7.3 days vs. mezlocillin 4grX4 + gentamicin 1.5mg/kgX3 for 7.2 days. In addition to antibiotic treatment all patients operated
Outcomes	Overall mortality Treatment failure (clinical) Fever, treatment and hospitalization duration
Notes	USA No outcomes in subgroups

Risk of bias

Yellin 1993 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By table of random numbers
Allocation concealment (selection bias)	Low risk	Central randomization at the research pharmacy
Incomplete outcome data (attrition bias) Mortality	High risk	90 out of 149 randomized patients were evaluated for mortality outcome
Incomplete outcome data (attrition bias) Failure	High risk	90 out of 149 randomized patients were evaluated for failure outcome
Other bias	Unclear risk	No fixed time for outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The clinician was kept blinded throughout the study

RCT - randomized controlled trial

vs - versus

Semi-empirical - comparison of second-line antibiotic treatment, given following establishment of microbiological or clinical diagnosis.
Treatment duration represents means unless otherwise specified.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alvarez-Lerma 2001b	Beta-lactam-aminoglycoside combination treatment versus beta-lactam-aminoglycoside combination treatment.
Badaro 2002	Allocation to additional aminoglycoside treatment not randomized. Patients were randomized to treatment with beta-lactam monotherapy versus 'standard' antibiotic treatment, which was a beta-lactam with or without an aminoglycoside.
Benlloch 1995	Antibiotic regimens incompatible with protocol. Randomization to 3 arms: 1) beta-lactam-aminoglycoside-nitroimidazole combination 2) beta-lactam-aminoglycoside combination 3) double beta-lactam combination.
Blumer 2003	No sepsis in inclusion criteria. Study included patients with acute exacerbation of cystic fibrosis, but the definition of exacerbation does not answer the criteria for sepsis as defined in review.
Bodey 1976	Study includes 100% patients with neutropenia.
Cetto 1983	Study includes 71% patients with neutropenia.
Chaudhary 2008	Sepsis was not mandated for inclusion to the study. Patients with bronchitis were included.

Study	Reason for exclusion
Chaudhary 2009	Sepsis was not mandated for inclusion to the study. Patients with bronchitis were included.
Ciftci 1997	Antibiotic regimens incompatible with protocol. Randomization to 4 arms: 1) beta-lactam-aminoglycoside-lincosamide combination 2) beta-lactam-aminoglycoside-imidazole combination 3) beta-lactam monotherapy 4) beta-lactam-imidazole combination.
Crenshaw 1983	Prophylaxis study. Randomization to beta-lactam monotherapy versus beta-lactam aminoglycoside combination therapy as preventive therapy for patients with penetrating abdominal wounds requiring surgical intervention.
Croce 1993	Not a randomized trial. Monotherapy and combination therapy groups were studied consecutively.
De Louvois 1992	Included patients were newborns with suspected sepsis.
Extermann 1995	Randomization to beta-lactam monotherapy versus best-guess antibiotic treatment as chosen by physician. The best guess treatment group includes monotherapy and various combinations.
Fainstein 1983	Study includes 62.5% neutropenic patients. The study randomized 321 episodes, of which 275 were evaluable - 172 in neutropenic patients and 103 episodes in non-neutropenic patients. Although analysis was intended to be separated, the number of evaluated patients in each group, is not separated to neutropenic and non-neutropenic patients. Although outcomes (death and failures) are given for non-neutropenic patients, the number of patients in the group is unknown. Information was unavailable from authors.
Fernandez 1991	Randomization to beta-lactam monotherapy versus combination therapy commonly used in specific centre (multicentre trial). Combinations consisted of different beta-lactams with aminoglycoside antibiotics in 211/273 patients evaluated in the combination group, and other antibiotic combinations in 62/273 patients. Outcomes are given per specific combination (failure), but the study is excluded since the decision as to which combination the patient received was left to the care-taker.
Foord 1985	Not a randomized trial. Article describes all patients on Glaxo data files who have been administered Ceftazidime monotherapy in comparative and non-comparative trials. No references in the article.
Gentry 1980	Not a randomized trial. Study describes centre's experience with monotherapy versus combination therapy. One study group was previously reported. All prospective, comparative, but no mention of randomization.
Gentry 1984	Prophylaxis study. Randomization to 3 arms (2 beta-lactam monotherapy arms and 1 beta-lactam-aminoglycoside combination therapy arm), as perioperative prophylaxis for patients with penetrating injuries of the abdomen.
Gentry 1985	Pooled analysis of patients with skin, soft-tissue and bone infections, comparing ceftazidime monotherapy to control regimens, including ticalcillin and tobramycin combination therapy. However, randomized patients cannot be separate from those who entered open comparative trials.
Gerber 1989	Prophylaxis study. Antibiotic treatment was administered as prophylaxis and patients did not fulfil the criteria for sepsis when randomized.
Gilbert 1998	Study includes 18% neutropenic patients (32/175 evaluable patients). In addition neutropenic patients were not randomized - all were allocated only to the combination regimen. Outcome data was unavailable separating randomized from non randomized (neutropenic) patients.
Giraud 1989	Antibiotic regimens incompatible with protocol. Randomization to 2 arms: 1) beta-lactam monotherapy versus 2) beta-lactam-aminoglycoside-nitroimidazole triple combination therapy.

Study	Reason for exclusion
Gold 1985	No sepsis in inclusion criteria. Study included patients with acute exacerbation of cystic fibrosis, but the definition of exacerbation does not answer the criteria for sepsis as defined in review.
Gomez 1990b	Observational study according to author correspondence.
Greco 1989	Non-randomized prospective comparative trial.
Gribble 1983	Study includes 60% neutropenic patients (30/50 evaluable episodes).
Haffejee 1984	Included patients were neonates and children.
Hall 1988	Included patients were neonates.
Hammerberg 1989	Included patients were premature neonates with risk factors for sepsis (31/72 patients between ages 0-1 months).
Hanson 1982	Antibiotic regimens incompatible with protocol. Combination therapy versus combination therapy.
Hoogkamp 1983	Not a randomized trial. Study groups were studied sequentially. In addition study population consists of cystic fibrosis patients with an exacerbation - sepsis not part of inclusion criteria.
Iakovlev 1997	Aminoglycoside was added only to patients that did not respond to the initial beta-lactam monotherapy that was administered empirically.
Iakovlev 2000	Not a randomized trial.
Iakovlev 2006	Study compares meropenem to "standard regimen" for sepsis at the study hospital (beta-lactams and fluoroquinolones in combination with aminoglycosides and/or metronidazole).
Ker 1989	Prophylaxis study. Randomization to prophylactic antibiotic treatment, patients did not fulfil criteria for sepsis when randomized.
Krumpe 1999	Patients first stratified by disease severity to monotherapy (severe disease) or combination therapy. Following stratification, the patients were randomized to 4 arms: 1) quinolone monotherapy 2) 'standard monotherapy' from a defined choice of various beta-lactams, at investigator's discretion 3) quinolone-beta-lactam combination therapy 4) 'standard combination therapy' which consisted of various possible combinations of beta-lactams and aminoglycosides at investigators discretion.
Ludwig 1980	Description of two separate randomized trials: 1) beta-lactam versus aminoglycoside 2) beta-lactam versus beta-lactam. All administered as monotherapies.
Maller 1991	Randomization to once daily aminoglycoside treatment versus twice daily aminoglycoside treatment. In addition to the aminoglycoside, a beta-lactam was administered if considered necessary. Administration of the beta-lactam not randomized (interim analysis of a multicentre study).
Mangi 1988	Randomization to beta-lactam monotherapy versus combination. The combination group consisted of clindamycin-aminoglycoside or beta-lactam-aminoglycoside combinations. The decision as to which combination treatment was administered was made on a case-by-case basis, according to the sputum's Gram stain. Patients with Gram-negative bacilli in the sputum were administered the beta-lactam based combination while all others received the clindamycin-based regimen. Outcomes for the two different combination treatments are given together.
McArdle 1987	Prophylaxis study. Randomization to beta-lactam monotherapy versus beta-lactam aminoglycoside combination therapy for prophylaxis prior to high-risk biliary tract surgery.

Study	Reason for exclusion
McCarty 1988	No sepsis in inclusion criteria. Study included patients with acute exacerbation of cystic fibrosis, but the definition of exacerbation does answer the criteria for sepsis as defined in review.
McLaughlin 1983	No sepsis in inclusion criteria. Study included patients with acute exacerbation of cystic fibrosis, but the definition of exacerbation does answer the criteria for sepsis as defined in review.
Mondorf 1987	Infection or sepsis not mentioned as part of inclusion criteria. Patients were randomized to receive beta-lactam monotherapy versus beta-lactam-aminoglycoside combination therapy, and the only outcome given is urinary enzyme excretion.
Mondorf 1989	No outcomes relevant for this review. The study randomized patients with severe infections to beta-lactam monotherapy versus beta-lactam aminoglycoside combination therapy. The only outcomes given are renal functions, mainly urinary enzyme levels, and mean serum creatinine per group. Author contacted to ask number of patients per group developing nephrotoxicity and other outcomes - but did not respond.
Moreno-Martinez 1998	Comparison of oral cefixime versus oral amoxicillin and intramuscular netilmicin. By protocol only intravenously administered beta-lactams are included.
Mouton 1985	Study published as conference proceeding, comparative without mention on randomization. No further details regarding the study were available.
Oblinger 1982	Randomization to beta-lactam monotherapy versus combination of antibiotics as deemed appropriate by the attending physicians.
Odio 1987	Included patients were neonates with proven invasive bacterial infections.
Padoan 1987	Inclusion criteria did not mandate sepsis for all included patients. Study included patients with acute exacerbation of cystic fibrosis, but the definition of exacerbation does answer the criteria for sepsis as defined in review.
Paoletti 1989	Comparison between aminoglycoside monotherapy (netimicin) to beta-lactam-aminoglycoside combination therapy (ampicillin + netilmicin).
Pereira 2009	Study include patients with neutropenia and fever.
Rodloff 1998	Study randomized patients to imipenem monotherapy versus various combination regimens: beta-lactam-aminoglycoside, two beta-lactams, beta-lactam-beta-lactamsa inhibitor, beta-lactam-anaerobic agent and quinolone-anaerobic agent. Patients allocated to the combination group were analysed as one group.
Romanelli 2002	Study randomized patients to beta-lactam monotherapy versus macrolide-aminoglycoside or macrolide-beta-lactam combination therapy.
Schoengut 1983	Non-randomized, prospective comparative trial.
Schuler 1995	Randomization to meropenem versus cefotaxime monotherapy. Aminoglycoside added to the cefotaxime arm for urinary tract infections and metronidazole added to the cefotaxime arm when anaerobic infection was suspected. These additions were performed non-randomly, by protocol.
Scott 1987	Randomization to 3 arms comparing beta-lactam monotherapy versus beta-lactam-metronidazole-aminoglycoside triple combination therapy versus beta-lactam-metronidazole combination therapy.
Sexton 1984	ICAAC abstract. Twenty-two patients were enrolled in a prospective randomized trial, and 8 patients received monotherapy in an open study. Results are shown for all 30 patients combined. Author contacted and replied that original data are no longer available, and therefore randomized pa-

Study	Reason for exclusion
	tients cannot be separated from the non-randomized. However, results of these trials were pooled with other trials and are described in Gentry 1985.
Sheftel 1986	No relevant outcomes for this review. The study randomized patients with osteomyelitis and provides outcomes only for evaluated patients at a follow up range of 2-38 months (appropriate for the type of infection). The number of randomized patients is unknown and outcomes at 30-days were unavailable.
Smith 1999	No sepsis in inclusion criteria. Study included patients with acute exacerbation of cystic fibrosis, but the definition of exacerbation does answer the criteria for sepsis as defined in review.
Solberg 1995	Article describes results from 4 separate trials. Randomization to meropenem versus ceftazidime monotherapy. An aminoglycoside was added to patients allocated to ceftazidime when resistance to ceftazidime and severe infections were suspected.
Solomkin 1986	Inadequate methodology. A publication stating that 'case report forms from an open multicentre study were reviewed': 69 patients assigned to ceftazidime and 66 patients assigned to ticarcillin and tobramycin with soft tissue infections are reported. Information obtained through author contact: these were the only arms of the trial, all patients included in the trial are reported in the publication, and this is the only report of the trial. However, according to the author, the study was not well designed and considered more as a collection of case reports, as stated in the publication.
Stack 1985	No sepsis in inclusion criteria. Study included patients with acute exacerbation of cystic fibrosis, but the definition of exacerbation does answer the criteria for sepsis as defined in review.
Tally 1986	Randomization to beta-lactam monotherapy (moxalactam) versus another beta-lactam (cefoxitime). An aminoglycoside could be added to the cefoxitime arm by the attending physician's decision, in consultation with an infectious diseases consultant.
Thompson 1980	Oral versus intravenous antibiotic administration. Study randomized women with PID to monotherapy of oral amoxicillin versus combination therapy consisting of IV penicillin + IV gentamicin. Inclusion criteria for the review specify IV administration of the beta-lactam in both arms.
Vazquez 1994	Prophylaxis study. Antibiotic treatment administered for prophylaxis, without sepsis. In addition trial is probably not randomized.
Vetter 1987	No sepsis in inclusion criteria. Study randomized patients with acute exacerbations of chronic bronchitis. Only 19/102 included patients were febrile.
Vetter 1992	Comparison of monotherapy (meropenem) versus monotherapy (ceftazidime)
Watanakunakorn 1997	Non-randomized comparison of penicillin versus penicillin + gentamicin for Staphylococcus aureus endocarditis.
Yildirim 2008	Study included children with neutropenic fever.

Characteristics of ongoing studies [ordered by study ID]

Aziz 2012

Trial name or title	Comparison of Ampicillin/Sulbactam versus Ampicillin/Gentamicin for Treatment of Intrapartum Chorioamnionitis: A Randomized Controlled Trial
Methods	Randomized controlled trial, double-blind

Aziz 2012 (Continued)

Participants	Pregnant women in labor or undergoing induction of labor diagnosed with chorioamnionitis
Interventions	<p>Unasyn 3 grams intravenously every six hours, plus intravenous normal saline placebo dose every eight hours until 24 hours post delivery</p> <p>versus</p> <p>Gentamicin 1.5 mg/kg intravenously every eight hours plus ampicillin 2 grams intravenously every six hours until 24 hours post delivery</p>
Outcomes	<ul style="list-style-type: none"> Proportion of participants in each arm experiencing treatment failure as indicated by resolution of maternal infection Maternal adverse events Neonatal adverse outcomes Cost
Starting date	May 2009
Contact information	Principal Investigator: Natali Aziz, MD, Stanford University
Notes	Estimated completion date: May 2014

DATA AND ANALYSES
Comparison 1. Monotherapy versus combination therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	44		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Same BL	13	1431	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.30]
1.2 Different BL	31	4146	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.71, 1.01]
2 All-cause mortality by study groups	41		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Same sepsis	7	839	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.75, 1.55]
2.2 Same abdominal	2	331	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.54, 1.55]
2.3 Same UTI	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Different sepsis	21	3298	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 0.99]
2.5 Different abdominal	6	550	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.56, 2.15]
2.6 Different UTI	4	298	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.21]
3 Clinical failure	66		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Same BL	20	1870	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.95, 1.29]
3.2 Different BL	46	4933	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.67, 0.84]
4 Clinical failure by study groups	61		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Same sepsis	12	1196	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.01, 1.55]
4.2 Same abdominal	2	308	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.80, 1.32]
4.3 Same UTI	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.46, 2.09]
4.4 Different sepsis	31	3743	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.81]
4.5 Different abdominal	10	731	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.18]
4.6 Different UTI	5	459	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.65, 1.91]
5 UTI relapse or reinfection	6	458	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.61, 1.67]
6 Bacteriological failure—all	44		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Same BL	15	801	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.87, 1.48]
6.2 Different BL	29	2760	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.69, 0.94]
7 Bacterial superinfection	28	3135	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 0.99]
8 Fungal superinfection	11	1119	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.42, 1.48]
9 Bacterial colonization	14	1635	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.65, 1.10]
10 Bacterial colonization—surveillance cultures	6	751	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.60, 1.01]
11 Development of bacterial resistance	9	1370	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.54, 1.45]
12 Any adverse event	40	5001	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.01]
13 Adverse events requiring treatment discontinuation	20	3098	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.52, 1.52]
14 Any nephrotoxicity	46	5269	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.23, 0.39]
14.1 Once-daily aminoglycoside	5	865	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.06, 0.53]
14.2 Twice-daily aminoglycoside	7	1127	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.24, 0.77]
14.3 Thrice-daily aminoglycoside	24	2138	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.20, 0.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.4 Non-specified amino-glycoside regimen	10	1139	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.19, 0.58]

Analysis 1.1. Comparison 1 Monotherapy versus combination therapy, Outcome 1 All-cause mortality.

Analysis 1.2. Comparison 1 Monotherapy versus combination therapy, Outcome 2 All-cause mortality by study groups.

Analysis 1.3. Comparison 1 Monotherapy versus combination therapy, Outcome 3 Clinical failure.

Analysis 1.4. Comparison 1 Monotherapy versus combination therapy, Outcome 4 Clinical failure by study groups.

Analysis 1.5. Comparison 1 Monotherapy versus combination therapy, Outcome 5 UTI relapse or reinfection.

Analysis 1.6. Comparison 1 Monotherapy versus combination therapy, Outcome 6 Bacteriological failure—all.

Analysis 1.7. Comparison 1 Monotherapy versus combination therapy, Outcome 7 Bacterial superinfection.

Analysis 1.8. Comparison 1 Monotherapy versus combination therapy, Outcome 8 Fungal superinfection.

Analysis 1.9. Comparison 1 Monotherapy versus combination therapy, Outcome 9 Bacterial colonization.

Analysis 1.10. Comparison 1 Monotherapy versus combination therapy, Outcome 10 Bacterial colonization—surveillance cultures.

Analysis 1.11. Comparison 1 Monotherapy versus combination therapy, Outcome 11 Development of bacterial resistance.

Analysis 1.12. Comparison 1 Monotherapy versus combination therapy, Outcome 12 Any adverse event.

Analysis 1.13. Comparison 1 Monotherapy versus combination therapy, Outcome 13 Adverse events requiring treatment discontinuation.

Analysis 1.14. Comparison 1 Monotherapy versus combination therapy, Outcome 14 Any nephrotoxicity.

Comparison 2. Monotherapy versus combination therapy (subgroup analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (Gram-negative infection)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Same BL	3	117	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.08, 4.07]
1.2 Different BL	5	313	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.80, 1.95]
2 All-cause mortality (Gram-negative bacteraemia)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Same BL	3	85	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.30, 8.75]
2.2 Different BL	2	125	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.63, 2.70]
3 All-cause mortality (non-urinary tract infection)	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Same BL	4	401	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.31]
3.2 Different BL	13	1458	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.52, 0.95]
4 All-cause mortality (Gram-positive infection)	3	188	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.12, 1.58]
5 Clinical failure (Gram-negative infection)	28		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Same BL	10	432	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.90, 1.68]
5.2 Different BL	18	1403	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.09]
6 Clinical failure (<i>Pseudomonas aeruginosa</i> infection)	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Same BL	6	124	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.68, 1.51]
6.2 Different BL	12	302	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.80, 1.82]
7 Clinical failure (Gram-negative bacteraemia)	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Same BL	4	101	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.45, 2.56]
7.2 Different BL	7	198	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.38, 1.48]
8 Clinical failure (bacteraemia)	22		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Same BL	5	141	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.77, 2.66]
8.2 Different BL	17	624	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.89]
9 Clinical failure (urinary tract infection)	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Same BL	4	84	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.59, 2.13]
9.2 Different BL	13	708	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.80, 1.87]
10 Clinical failure (non-urinary tract infection)	44		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Same BL	10	1248	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.99, 1.42]
10.2 Different BL	34	3132	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.59, 0.78]
11 Clinical failure (Gram-positive infection)	5	305	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.40, 1.19]
12 Need for operation (endocarditis)	4	243	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Bacteriological failure (Gram-positive infection)	5	300	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.47, 1.69]

Analysis 2.1. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 1 All-cause mortality (Gram-negative infection).

Analysis 2.2. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 2 All-cause mortality (Gram-negative bacteraemia).

Analysis 2.3. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 3 All-cause mortality (non-urinary tract infection).

Analysis 2.4. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 4 All-cause mortality (Gram-positive infection).

Analysis 2.5. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 5 Clinical failure (Gram-negative infection).

Analysis 2.6. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 6 Clinical failure (*Pseudomonas aeruginosa* infection).

Analysis 2.7. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 7 Clinical failure (Gram-negative bacteraemia).

Analysis 2.8. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 8 Clinical failure (bacteraemia).

Analysis 2.9. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 9 Clinical failure (urinary tract infection).

Analysis 2.10. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 10 Clinical failure (non-urinary tract infection).

Analysis 2.11. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 11 Clinical failure (Gram-positive infection).

Analysis 2.12. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 12 Need for operation (endocarditis).

Analysis 2.13. Comparison 2 Monotherapy versus combination therapy (subgroup analyses), Outcome 13 Bacteriological failure (Gram-positive infection).

Comparison 3. Monotherapy versus combination therapy (sensitivity analyses)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 All-cause mortality by allocation concealment	44		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 A same BL	6	1068	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.31]
1.2 B same BL	7	363	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.47, 2.30]
1.3 A different BL	12	2154	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]
1.4 B different BL	17	1878	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.53, 0.93]
1.5 C different BL	2	114	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.21]
2 All-cause mortality by allocation generation	44		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 A same BL	6	1068	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.31]
2.2 B same BL	7	363	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.47, 2.30]
2.3 A different BL	19	2957	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.09]
2.4 B different BL	10	1075	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.50, 1.04]
2.5 C different BL	2	114	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.21]
3 All-cause mortality by ITT versus per-protocol analysis	44		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 ITT—same BL (type one studies)	5	519	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.28, 1.19]
3.2 Per-protocol—same BL (type two and three studies)	6	761	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.80, 1.51]
3.3 Unknown—same BL (type four studies)	2	151	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.06, 13.25]
3.4 ITT—different BL (type one studies)	15	2989	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.07]
3.5 Per-protocol—different BL (type two and three studies)	12	1037	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.54, 1.07]
3.6 Unknown—different BL (type four studies)	4	120	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.21]
4 Clinical failure by allocation concealment	66		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 A same BL	8	1138	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.93, 1.32]
4.2 B same BL	12	732	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.79, 1.50]
4.3 A different BL	14	2099	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.86]
4.4 B different BL	29	2660	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.69, 0.93]
4.5 C different BL	3	174	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.92]
5 Clinical failure by allocation generation	66		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 A same BL	9	1319	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.29]
5.2 B same BL	11	551	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.83, 1.69]
5.3 A different BL	26	3288	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.66, 0.88]
5.4 B different BL	17	1471	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.63, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5 C different BL	3	174	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.92]
6 Clinical failure by blinding	66		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Non-blinded—same BL	19	1666	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.93, 1.35]
6.2 Any blinding—same BL	1	204	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.82, 1.37]
6.3 Non-blinded—different BL	40	3996	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.70, 0.91]
6.4 Any blinding—different BL	6	937	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.50, 0.77]
7 Clinical failure by ITT versus per-protocol analysis	66		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 ITT—same BL (type one)	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.43, 1.40]
7.2 ITT assuming failure for dropouts—same BL (type two)	9	902	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.09, 1.60]
7.3 Per-protocol—same BL (type three studies)	4	580	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.91, 1.33]
7.4 Type four studies—same BL	5	278	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.56, 1.61]
7.5 ITT—different BL (type one)	13	1589	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.60, 0.85]
7.6 ITT assuming failure for dropouts—different BL (type two)	14	2065	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.73, 0.94]
7.7 Per-protocol—different BL (type three studies)	12	1031	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.95]
7.8 Type four studies—different BL	7	248	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.52, 1.69]

Analysis 3.1. Comparison 3 Monotherapy versus combination therapy (sensitivity analyses), Outcome 1 All-cause mortality by allocation concealment.

Analysis 3.2. Comparison 3 Monotherapy versus combination therapy (sensitivity analyses), Outcome 2 All-cause mortality by allocation generation.

Analysis 3.3. Comparison 3 Monotherapy versus combination therapy (sensitivity analyses), Outcome 3 All-cause mortality by ITT versus per-protocol analysis.

Analysis 3.4. Comparison 3 Monotherapy versus combination therapy (sensitivity analyses), Outcome 4 Clinical failure by allocation concealment.

Analysis 3.5. Comparison 3 Monotherapy versus combination therapy (sensitivity analyses), Outcome 5 Clinical failure by allocation generation.

Analysis 3.6. Comparison 3 Monotherapy versus combination therapy (sensitivity analyses), Outcome 6 Clinical failure by blinding.

Analysis 3.7. Comparison 3 Monotherapy versus combination therapy (sensitivity analyses), Outcome 7 Clinical failure by ITT versus per-protocol analysis.

ADDITIONAL TABLES

Table 1. Beta lactam monotherapies

Monotherapy	No. studies	No. of participants treated	Doses (no. studies: dose)
ceftazidime	12	939	Four: 2 g × 2/d; five: 2 g × 3/d; one: 1 g × 4/d; one: 1 g × 3/d; one: NS
cefotaxime	Seven	281	One: 1 g × 4/d; one: 2 g × 6/d; one: 3 g × 3/d; 1 to 2 g × 4/d; one: 1 g × 2/d; one: 2 g × 6/d; one: 1 g × 3 to 4/d
imipenem	Six	580	Three: 500 mg × 4/d; one: 500 to 1000 mg × 4/d; one: 500 mg × 3/d; one: NS
cefoperazone	Six	238	Two: 2 g × 2/d; one: 2 g × 3/d; one: 6 g × 2/d; one: 1 to 4 g/d; one: 1.5 g × 4/d
meropenem	Five	376	Five: 1 g × 3/d
ceftriaxone	Three	237	Three: 2 g × 1/d; one: 2 g × 2/d
piperacillin-tazobactam	Three	269	One: 4 g × 4/d; one: 0.5 g × 4/d; two: 4.5 g × 3/d
cefepime	Three	160	One: 2 g × 3/d; two: 2 g × 2/d
ceftizoxime	Three	50	One: 60 to 150 mg/kg/d; one: 1 to 2 g × 3/d; one: 20 to 50 mg/kg × 2 to 3/d
mezlocillin	Three	47	One: 4 g × 4/d; one: 62.5 mg/kg × 4/d; one: 10 g × 3/d
piperacillin	Two	83	Two: 3 g × 6/d
amoxicillin-clavulanate	Two	81	One: 2.2 gr × 3/d; one: NS
ampicillin	Two	44	One: 25 mg/kg × 4/d, one: 500 mg × 4/d
cefazoline	One	58	One: 1 g × 3/d
amoxicillin-sulbactam	One	56	One: 33 mg/kg × 3/d

Table 1. Beta lactam monotherapies (Continued)

cefoxitin	One	31	One: 2 g × 3/d
carbenicillin	One	25	One: 10 g × 3/d
ticarcillin-clavulanic acid	One	21	One: 3.1 g × 4 to 6/d
azlocillin	One	20	One: 13 + -2.2 gr/d
moxalactam	One	18	One: 2 g × 3/d
Gram-positive infection			
oxacillin	One	12	One: 12 g/d
cloxacillin	One	45	One: 2 g × 6/d
cefamandole	One	36	One: 2 g × 3/d
nafcillin	One	33	One: 1.5 to 6 g × 6/d
ceftriaxone	One	67	One: 2 g × 1/d

APPENDICES

Appendix 1. Search strategy for CENTRAL, The Cochrane Library

#1 MeSH descriptor beta-Lactams, this term only
 #2 MeSH descriptor Penicillins, this term only
 #3 MeSH descriptor Cephalosporins, this term only
 #4 MeSH descriptor Carbapenems, this term only
 #5 MeSH descriptor Imipenem, this term only
 #6 MeSH descriptor Ceftazidime, this term only
 #7 MeSH descriptor Cefotaxime, this term only
 #8 MeSH descriptor Amoxicillin-Potassium Clavulanate Combination, this term only
 #9 beta-lactam*:ti,ab
 #10 co?amoxiclav* or cephalosporin* or ceftazidim* or cefotaxim* or carbapenem* or imipenem* or meropenem*
 #11 beta-lactam* near (combin* or mono*)
 #12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
 #13 MeSH descriptor Aminoglycosides, this term only
 #14 (aminoglycoside* or netilmicin* or gentamicin* or amikacin* or tobramycin* or streptomycin* or isepamicin* or sisomicin* or combinat*):ti,ab
 #15 (#13 OR #14)
 #16 (#12 OR (#12 AND #15))
 #17 MeSH descriptor Pneumonia, this term only
 #18 MeSH descriptor Sepsis, this term only
 #19 MeSH descriptor Shock, Septic, this term only
 #20 MeSH descriptor Bacteremia explode all trees
 #21 MeSH descriptor Infection, this term only
 #22 MeSH descriptor Endocarditis, Bacterial explode all trees
 #23 MeSH descriptor Endocarditis, this term only
 #24 MeSH descriptor Staphylococcus, this term only
 #25 MeSH descriptor Streptococcus, this term only
 #26 (pneumonia* or infect* or sepsis* or septic* or bacter*):ti,ab
 #27 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
 #28 (#16 AND #27)

Appendix 2. Search strategy for MEDLINE (Ovid SP)

1. Beta-Lactams/ or Penicillins/ or Cephalosporins/ or Carbapenems/ or Imipenem/ or Ceftazidime/ or Cefotaxime/ or Amoxicillin-Potassium Clavulanate Combination/ or beta-lactam*.ti,ab. or (co?amoxiclav* or cephalosporin* or ceftazidim* or cefotaxim* or carbapenem* or imipenem* or meropenem*).mp. or (beta-lactam* adj5 (combin* or mono*)).mp.
2. Aminoglycosides/ or (aminoglycoside* or netilmicin* or gentamicin* or amikacin* or tobramycin* or streptomycin* or isepamicin* or sisomicin* or combinat*).ti,ab. or Drug-Therapy-Combination/
3. 1 or (1 and 2)
4. pneumonia/ or exp Sepsis/ or Shock, Septic/ or exp Bacteremia/ or Infection/ or exp Endocarditis, Bacterial/ or Endocarditis/ or exp Endocarditis, Subacute Bacterial/ or Staphylococcus/ or Streptococcus/ or (pneumonia* or infect* or sepsis* or septic* or bacter*).ti,ab.
5. 3 and 4
6. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
7. 6 and 5

Appendix 3. Search strategy for EMBASE (Ovid SP)

1. beta lactam/ or penicillin derivative/ or cephalosporin derivative/ or carbapenem derivative/ or imipenem/ or ceftazidime/ or cefotaxime/ or amoxicillin plus clavulanic acid/ or beta-lactam*.ti,ab. or (co?amoxiclav* or cephalosporin* or ceftazidim* or cefotaxim* or carbapenem* or imipenem* or meropenem*).mp. or (beta-lactam* adj5 (combin* or mono*)).mp.
2. aminoglycoside/ or (aminoglycoside* or netilmicin* or gentamicin* or amikacin* or tobramycin* or streptomycin* or isepamicin* or sisomicin* or combinat*).ti,ab. or drug combination/
3. 1 or (1 and 2)
4. pneumonia/ or exp sepsis/ or septicemia/ or bacteremia/ or infection/ or exp bacterial endocarditis/ or endocarditis/ or Staphylococcus/ or Staphylococcus/ or (pneumonia* or infect* or sepsis* or septic* or bacter*).ti,ab.
5. 4 and 3
6. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals not (humans and animals)).sh.
7. 5 and 6

Appendix 4. Search strategy for LILACS (via BIREME)

(co?amoxiclav\$ or cephalosporin\$ or ceftazidim\$ or cefotaxim\$ or carbapenem\$ or imipenem\$ or meropenem\$ or beta-lactam \$) and (aminoglycoside\$ or netilmicin\$ or gentamicin\$ or amikacin\$ or tobramycin\$ or streptomycin\$ or isepamicin\$ or sisomicin\$ or combinat\$ or pneumonia\$ or infect\$ or sepsis\$ or septic\$ or bacter\$ or endocardit\$ or Staphylococ\$ or Streptococ\$) and (trial\$ or Random \$ or placebo\$ or ((single or double or triple) and (blind\$ or mask\$)) or (ensayo controlado) or (experimentação controlada) or multicenter or multicentre or prospective or (estudio anticipado) or (estudo em perspectiva))

FEEDBACK

Obtaining data on all-cause mortality, 16 June 2013

Summary

Thank you for taking on the large amount of data surrounding topic of aminoglycoside and beta-lactam combination therapy in the treatment of sepsis. With the large volume of studies spanning such a long time period this was no small task. With this in mind we still have some one question regarding the primary outcome analysis of all cause mortality between the two treatment arms.

The primary mortality analysis contained 43 of the total 64 studies included in the review and they were split into two separate subgroups, using either the same or a different beta-lactam agent as monotherapy as in combination therapy. Our concern is centered on the outstanding 21 studies not included in this analysis. We were wondering what attempts were made to collect mortality data from these remaining trials questioning whether the inclusion of those results would statistically alter the outcomes. We understand that a number of these studies were completed over 40 years ago and the data may be very difficult to obtain.

In the subgroup where a different beta-lactam was used the risk of mortality was non-significantly lowered in the monotherapy arm RR 0.85 (95% CI 0.71, 1.01). With the results being close to statistical significance we were wondering if the addition of data from the outstanding studies would actually make a statistical difference. If this were truly the case then your conclusion of "The addition of an aminoglycoside to beta-lactams for sepsis should be discouraged. All-cause fatality rates are unchanged. Combination treatment carries a significant risk of nephrotoxicity" would change and the call to avoid the use of these antibiotics would be much stronger.

We also pooled all of the data from both subgroups (same and different beta-lactams) and found that it did not change the results of the different beta-lactam group but greatly narrowed the confidence interval of the same beta-lactam group with a RR of 1.13 (0.97, 1.31) - increased risk of mortality in the combination group versus monotherapy. With this analysis we also found very little heterogeneity between same and different beta-lactam studies ($I^2 = 8\%$).

We understand the beta-lactam agent selected, specifically in regards the spectrum of activity, greatly impacts the effects of empirical therapy but with this potentially increased risk of mortality that is consistent across this large number of studies leads us to believe that although statistically non-significant it seems plausible that the risk of mortality with combination therapy over beta-lactam monotherapy is real.

We also believe that the possibility of “emotional based medicine” is real in this patient population. As the majority of these studies were open-label despite being randomized, it is not unlikely that “sicker” patients would receive more drugs (i.e. combination therapy). If this were true then it is plausible that patients who were more likely to die received more antibiotics and were in the combination groups but with the effect remaining relatively consistent across this large number of studies, we feel that a true risk may actually exist.

After this long discussion, our question returns to whether or not mortality data are available from the remaining 21 studies and what attempts have been made to retrieve this information. A statistically significant increase in mortality, along with the increase in adverse events seen with combination therapy would likely facilitate a rapid change in practice and removal of this therapeutic option. Just as an exercise we inserted the data provided by your review into Review Manager to test how many events it would take to make the difference in mortality. We understand this is not a truly scientific exercise but one based on curiosity.

What we found was that when we added two events (deaths) to the combination group in the most heavily weighted study ([Felisart 1985](#)) the outcome of mortality became statistically significantly higher in the combination group. We also combined all of the data between the same different beta-lactam subgroups and found that only eight more deaths in the combination group made the entire analysis (all 43 studies) statistically significant for an increase in mortality in the combination group. On the flip side, it took 80 events in the monotherapy group to swing the analysis the other way and statistically favour combination therapy in the outcome of mortality.

Thank you for your time

Reply

Dear Dr Amadio,

Thank you for your kind attention to our work and your input for the data analysis.

In response to your question regarding obtaining data on all-cause mortality, we mailed all authors of trials that did not report on this outcome asking for the data, as is routine in Cochrane reviews. We agree with you on the importance of the missing data on mortality and for this reason we made extra efforts to obtain the data. If we did not establish contact with the corresponding author, we tried to contact a second and third author. The data presented in our review are the result of this process and still we miss mortality data from a third of all randomized controlled trials (RCTs) that were conducted.

Selection bias should not occur in adequately conducted RCTs, those using appropriate allocation concealment. Allocation concealment is the procedure ensuring that no one is aware of the treatment assignment when the patient is recruited into the trial and before the patient is allocated to an intervention. We observed in our review that the advantage to combination therapy was larger in trials with unclear methods for allocation concealment (studies not reporting the methods for this procedure) compared to trials that used methods ensuring adequate allocation concealment. Therefore, it is possible that results were affected by selection of sicker patients to the combination therapy group. However the difference between trials with low and unclear risk of bias was not statistically significant and we have no actual data on whether bias could occur in the trials with unclear risk of bias. Most importantly to our view, the trials comparing different beta-lactams usually compared a new, broad-spectrum beta-lactam to an old, classical regimen; we believe that if selection bias crept in to some trials it would have worked in the opposite direction of recruiting the sicker patients to the novel monotherapy arm. The fact that most of the trials were open, might have led to a different type of bias, and dilution of effects, because physicians could add an aminoglycoside to failing patients in the monotherapy arm, while this could not occur in the combination therapy arm.

Methods exist to formally examine the possible effects of missing data in meta-analysis. We will consider adding such an analysis to an update of our review. More importantly, we will highlight the issue of missing data on all-cause mortality. Should your important correspondence result in any authors sending further data from their trials on mortality, these will be added to our review.

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Reply

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WHAT'S NEW

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 1, 2006

Date	Event	Description
20 December 2013	New citation required but conclusions have not changed	Our updated review reached the same conclusions as Paul 2006 . The added trials did not change the direction or the magnitude of results. We have added Summary of finding tables to the current update and have graded the quality of evidence for the main outcomes. Karla Soares-Weiser has left and Adi Lador has joined the review author team.
20 December 2013	New search has been performed	This review is an update of the previous Cochrane systematic review (Paul 2006), which included 64 RCTs. Five new trials were added in the current update; three were published after the previous review (Banasal 2006 ; Damas 2006 ; Hasali 2005), one was awaiting assessment in the previous review (Figueroa-Damian 1996) and one was newly identified (García Ramírez 1999).
13 August 2013	Feedback has been incorporated	Feedback submitted and responded to. Two Cochrane references updated and typos corrected.
2 September 2008	New citation required but conclusions have not changed	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Mical Paul (MP): performed the search and scanned abstracts; retrieved full-text articles and applied inclusion and exclusion criteria; performed risk of bias assessment, data extraction and analysis. MP communicated with authors and wrote the protocol and the review.

Adi Lador (AL): performed an update search (2011) and scanned the new abstracts; retrieved full-text articles and applied inclusion and exclusion criteria; performed risk of bias assessment, data extraction and analysis for the updated search; and wrote the updated review.

Simona Grozinsky-Glasberg (SG-G): extracted the data for the first version of this review; and reviewed and approved the final version of the updated review.

Leonard Leibovici (LL): assisted with inclusion and exclusion of studies; performed quality assessment, data extraction and analysis; assisted with communication with authors; and assisted with the writing and review of all versions of the protocol and the review.

DECLARATIONS OF INTEREST

Mical Paul: none known.

Adi Lador: none known.

Simona Grozinsky-Glasberg: none known.

Leonard Leibovici: none known.

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of this review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

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INDEX TERMS

Medical Subject Headings (MeSH)

Aminoglycosides [adverse effects] [*therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Bacterial Infections [*drug therapy]; Cause of Death; Drug Therapy, Combination [methods]; Gram-Negative Bacterial Infections [drug therapy]; Gram-Positive Bacterial Infections [drug therapy]; Randomized Controlled Trials as Topic; beta-Lactams [*therapeutic use]

MeSH check words

Humans