Cochrane Library

Cochrane Database of Systematic Reviews

Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients (Review)

Vidal L, Ben dor I, Paul M, Eliakim-Raz N, Pokroy E, Soares-Weiser K, Leibovici L

Vidal L, Ben dor I, Paul M, Eliakim-Raz N, Pokroy E, Soares-Weiser K, Leibovici L.
Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients.
Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD003992.
DOI: 10.1002/14651858.CD003992.pub3.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients

Liat Vidal[1], Itsik Ben dor[1], Mical Paul[2], Noa Eliakim-Raz[1], Ellisheva Pokroy[3], Karla Soares-Weiser[4], Leonard Leibovici[1]

[1]Department of Medicine E, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel. [2]Division of Infectious Diseases, Rambam Health Care Campus, Haifa, Israel. [3]Department of Medicine A, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel. [4]Cochrane Editorial Unit, Cochrane, London, UK

Contact: Liat Vidal, Department of Medicine E, Beilinson Hospital, Rabin Medical Center, 39 Jabotinski Street, Petah Tikva, 49100, Israel. vidallit@yahoo.com, VidalL2@clalit.org.il.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 9, 2016.

Citation: Vidal L, Ben dor I, Paul M, Eliakim-Raz N, Pokroy E, Soares-Weiser K, Leibovici L. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD003992. DOI: 10.1002/14651858.CD003992.pub3.

ABSTRACT

Background

Fever occurring in a neutropenic patient remains a common life-threatening complication of cancer chemotherapy. The common practice is to admit the patient to hospital and treat him or her empirically with intravenous broad-spectrum antibiotics. Oral therapy could be an alternative approach for selected patients.

Objectives

To compare the efficacy of oral antibiotics versus intravenous (IV) antibiotic therapy in febrile neutropenic cancer patients.

Search methods

The Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 1) in The Cochrane Library, MEDLINE (1966 to January week 4, 2013), EMBASE (1980 to 2013 week 4) and LILACS (1982 to 2007). We searched several databases for ongoing trials. We checked the conference proceedings of the Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) (1995 to 2007), and all references of included studies and major reviews were scanned.

Selection criteria

Randomised controlled trials (RCTs) comparing oral antibiotic(s) to intravenous antibiotic(s) for the treatment of neutropenic cancer patients with fever. The comparison between the two could be started initially (initial oral) or following an initial course of intravenous antibiotic treatment (sequential).

Data collection and analysis

Two review authors independently assessed trial eligibility and methodological quality and extracted data. Data concerning mortality, treatment failures and adverse events were extracted from the included studies assuming an 'intention-to-treat' basis for the outcome measures whenever possible. Risk ratios (RR) with 95% confidence intervals (CI) were estimated for dichotomous data. Risk of bias assessment was also made in line with methodology of The Cochrane Collaboration.

Main results

Twenty-two trials (3142 episodes in 2372 patients) were included in the analyses. The mortality rate was similar when comparing oral to intravenous antibiotic treatment (RR 0.95, 95% CI 0.54 to 1.68, 9 trials, 1392 patients, median mortality 0, range 0% to 8.8%). Treatment

failure rates were also similar (RR 0.96, 95% CI 0.86 to 1.06, all trials). No significant heterogeneity was shown for all comparisons but adverse events. The effect was stable in a wide range of patients. Quinolones alone or combined with another antibiotic were used with comparable results. Adverse reactions, mostly gastrointestinal, were more common with oral antibiotics.

Authors' conclusions

Based on the present data, oral treatment is an acceptable alternative to intravenous antibiotic treatment in febrile neutropenic cancer patients (excluding patients with acute leukaemia) who are haemodynamically stable, without organ failure, and do not have pneumonia, infection of a central line or a severe soft-tissue infection. The wide CI for mortality allows the present use of oral treatment in groups of patients with an expected low risk for mortality, and further research should be aimed at clarifying the definition of low risk patients.

PLAIN LANGUAGE SUMMARY

Oral antibiotics for treating febrile neutropenia in cancer patients at low risk for complications

Neutropenia (low white blood cell count) is a complication of cancer chemotherapy that exposes patients to life-threatening infections. Current practice for neutropenic patients with fever is hospital admission and treatment with intravenous antibiotics. Febrile neutropenia encompasses a spectrum of disease severity and low risk patients may be treated less aggressively. This review of randomised controlled trials showed comparable death and failure rates for oral and intravenous antibiotics for low risk patients, those with solid tumours or chronic leukaemia or lymphoma, and independent of age, source of infection and severity of the neutropenia.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Oral compared to intravenous antibiotic therapy for febrile neutropenia in cancer patients

Oral compared to intravenous antibiotic therapy for febrile neutropenia in cancer patients

Patient or population: patients with febrile neutropenia in cancer patients
Settings:
Intervention: oral
Comparison: intravenous antibiotic therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	intravenous antibiotic therapy	Oral				
Mortality	**Study population**		**RR 0.95** (0.54 to 1.68)	1392 (9 studies)	⊕⊕⊕⊖ **moderate** [2]	
	32 per 1000	**30 per 1000** (17 to 54)				
	Low risk					
	0 per 1000	**0 per 1000** (0 to 0)				
Treatment failure	**Study population**		**RR 0.96** (0.86 to 1.06)	3142 (22 studies)	⊕⊕⊕⊖ **moderate** [1]	
	284 per 1000	**272 per 1000** (244 to 301)				
	Moderate					
	211 per 1000	**203 per 1000** (181 to 224)				
Treatment failure - per protocol analysis	**Study population**		**RR 0.98** (0.86 to 1.11)	2912 (22 studies)	⊕⊕⊕⊖ **moderate** [1]	
	225 per 1000	**221 per 1000** (194 to 250)				

	Moderate				
	184 per 1000	**180 per 1000** (158 to 204)			
Adverse events requiring discontinuation of antibiotics	**Study population**		**RR 1.45** (0.61 to 3.46)	1823 (15)	⊕⊕⊝⊝ **low** [1, 2]
	21 per 1000	**31 per 1000** (13 to 73)			
	Moderate				
	0 per 1000	**0 per 1000** (0 to 0)			
Treatment failure not dt modification in update	**Study population**		**RR 0.95** (0.85 to 1.06)	3041 (21)	⊕⊕⊕⊝ **moderate** [1]
	267 per 1000	**254 per 1000** (227 to 283)			
	Moderate				
	180 per 1000	**171 per 1000** (153 to 191)			

*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

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.

[1] High risk of detection bias in most of the trials
[2] A wide CI

BACKGROUND

Patients with cancer who experience fever while being neutropenic are at risk of serious infections (Bodey 1966; Klaassen 2000a; Lucas 1996; Pizzo 1982; Rackoff 1996). Empirical use of antibiotics, based on previous practice without knowledge of the cause of infection, has lowered the incidence of death and serious complications (Schimpff 1971; Schimpff 1986, Talcott 1988; Viscoli 2002). Traditionally the practice is to admit and treat neutropenic patients empirically with intravenous (IV) broad-spectrum antibiotics at the emergence of a fever (Hughes 2002).

The empirical selection of an appropriate antibiotic is based on the patient's immune status (that is being neutropenic) as well as the suspected invading organism and its susceptibility to antibiotics. Neutropenic cancer patients form a heterogeneous group. A retrospective study indicated the existence of a patient subpopulation responding promptly to antibiotic therapy, thus raising the possibility of using different treatment strategies, such as oral therapy and outpatient treatment (Talcott 1988). In parallel, the pattern of pathogens (that is bacteria) in neutropenic patients with fever has changed, with a declining incidence of Gram-negative bacteraemia and increasing incidence of Gram-positive infections (EORTC 1990; Hann 1997; Hughes 2002), resulting in a change in antibiotic practice. Oral treatment became a viable option with the advent of new extended spectrum oral antibiotics. The potential of oral treatment and the deleterious effects of hospitalisation (with need for an intravenous access line, exposure to multi-drug resistant organisms) and greater awareness of the importance of quality of life and patient satisfaction, especially among cancer patients (Talcott 1994), has led to a re-evaluation of the approach to neutropenic febrile patients.

Research has therefore focused on methods to prospectively identify neutropenic patients with fever who are at low risk of complications. Several clinical prediction rules were developed and validated for children and adult populations at low risk (Klaassen 2000a; Klastersky 2000; Rackoff 1996; Talcott 1988; Talcott 1992). Talcott et al constructed four groups out of which one included patients with an expected low complications rate. The patients at low risk developed fever out of hospital, had controlled cancer and had no co-morbidity. The rule was validated prospectively and later tested in a pilot study for its ability to select patients for early switch from IV to oral treatment (Talcott 1992). A consensus panel, the Multinational Association for Supportive Care in Cancer (MASCC), developed a set of criteria that are predictors of good prognosis in 'low risk' adult patients: acquisition of fever out of hospital, age younger then 60 years, absent to moderate symptoms, no hypotension, no chronic bronchitis, and a background of either a solid tumour or haematological malignancy with no history of fungal infection; in a validated scoring system. While receiving conventional therapy patients with a score of equal to or greater than 21 had a low rate of serious medical complication (6%) and only 1% mortality (Klastersky 2000).

Simultaneously, clinical trials (Malik 1992; Rubenstein 1993) have examined the safety and feasibility of oral antibiotic treatment in selected patients. In the absence of an accepted definition there was no consistency in the selection of patients defined as a 'low risk' group. Most of these trials were small, single centre trials. Thus, although reporting similar rates of success for oral and intravenous therapy, the superiority of an intravenous regimen cannot be ruled out.

The most recent guidelines for antibiotic treatment in neutropenic patients with cancer (Hughes 2002) are very cautious regarding the use of oral antibiotics alone. They recommend careful selection of low risk patients and limit this approach to adults, of whom only some may receive the treatment at home.

In the present systematic review we intended to provide better evidence regarding the safety and efficacy of oral treatment as opposed to intravenous treatment. We tried to clarify the definitions of the low risk subgroup and the appropriate antibiotics for oral treatment as well as the limits of present knowledge.

OBJECTIVES

To compare the efficacy of oral antibiotics versus intravenous antibiotic therapy in febrile neutropenic cancer patients.

In addition, we compared the efficacy of these treatment modalities in the following subgroups.

- Patients with unexplained fever (versus documented infection).
- Patients with an absolute neutrophil count of more than 0.1 cells x 10^9/L (versus those with a lower neutrophil count).
- Patients with a solid tumour (versus those with a haematological malignancy).
- Patients 60 years old and under (versus those above 60 years).
- Children (according to trial definition) (versus adults).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing any oral antibiotics to any intravenous (IV) antibiotics for the treatment of febrile neutropenia in cancer patients. The oral antibiotics could be started at presentation in patients allocated to oral treatment (viz, initial oral) or as part of a sequential IV to oral strategy where all patients were initially treated intravenously and those allocated to oral treatment were switched to oral therapy after a predefined time independent of the neutropenic episode (viz., sequential).

Types of participants

Patients with cancer and chemotherapy-induced neutropenia or patients with cancer who underwent bone marrow transplantation who presented with fever.

Types of interventions

A comparison of the following.

(1) Any oral antibiotics, administered as a single drug or as a combination of orally administered antibiotics.
(2) Any antibiotics administered intravenously, either as monotherapy or combination therapy.

Studies in which patients were allocated to these regimens initially, before administration of any other antibiotics for the specific febrile episode (initial oral), were analysed separately from studies in

which intravenous antibiotics had been first given to all patients (that is sequential intravenous to oral therapy).

Types of outcome measures

Primary outcomes

- All cause mortality at 30 days follow-up
- Mortality caused by the infectious episode at end of follow-up (restricted to 30 days)
- Treatment failure (restricted to 30 days)

For the purpose of this review, treatment failure was defined as a composite endpoint comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention (Consensus panel 1990; Feld 1998).

Secondary outcomes

- Treatment failure not due to modification of the primary intervention
- Lost to follow-up before end of study (dropouts)

Adverse effects

- Life-threatening or associated with permanent disability
- Requiring discontinuation of therapy

Search methods for identification of studies

Electronic searches

Relevant trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 1) (Appendix 1), MEDLINE (1966 to January week 4, 2013) (Appendix 2), EMBASE (1980 to 2013 week 4) (Appendix 3) and LILACS (1982 to 2007) (Appendix 4).

Searching other resources

References of all identified studies as well as major reviews were inspected for more studies. We searched the following conference proceedings for unpublished trials: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (1995 to 2006); The American Society of Hematology (2001 to 2002) (available at http://www.hematology.org/). We searched the following trial databases for ongoing and unpublished trials: Current Controlled Trials in the metaRegister of controlled clinical trials (http://www.controlled-trials.com/); UKCCCR Register of Cancer Trials (www.ctu.mrc.ac.uk/ukcccr); PDQ (Physician Data Query) database of the National Cancer Institute (http://www.cancer.gov/search/clinical_trials/); and the National Institutes of Health database (http://clinicaltrials-nccs.nlm.nih.gov/).

Additionally, the first or corresponding author of each included study and pharmaceutical companies were contacted for complementary information or information regarding unpublished trials. Letters, abstracts and unpublished trials were accepted in order to reduce the influence of publication bias.

Data collection and analysis

Selection of studies

One review author inspected the abstract of each reference identified by the search and applied the inclusion criteria. For possibly relevant articles the full article was obtained and inspected by two review authors independently.

Data extraction and management

Two review authors independently extracted data from the included trials. In addition the third review author extracted data from 10% of the studies, selected randomly. Data extractions were discussed, decisions documented, and all authors of included studies were contacted for clarification. Justifications for excluding studies from the review were also documented. Differences in the data extracted were resolved by discussion. In the case of disagreement between the two review authors, a third review author extracted the data. All data were collected on an intention-to-treat (ITT) basis whenever possible.

Trials were identified by the name of the first author and year in which the trial was first published, and ordered chronologically. The following data were extracted, checked and recorded.

Characteristics of trials

- Date, location and setting of trial (inpatients or ambulatory patients)
- Publication status
- Case definitions used (inclusion and exclusion criteria)
- Design (intention to treat, method of randomisation and allocation)
- Unit of randomisation
- Sponsor of trial

Characteristics of patients

- Number of participants and number of episodes in each group
- Age (mean and SD, or median plus range)
- Underlying malignancy and malignancy status
- Site of infection (three most common)
- Disease severity measure: septic shock, confusion, respiratory, liver and renal impairment
- Percentage of patients with neutrophil count more than 0.1 cells x 10^9/L in each group
- Percentage of patients with a solid tumour or lymphoma and chronic leukaemia in each group
- Number of patients with unexplained fever in each group
- The three most common pathogens (Gram-negative bacteria, Gram-positive bacteria)
- Number of patients developing resistant superinfection or colonisation, or both
- Number of patients 60 years of age and younger
- Number of children (according to trial's definition)

Characteristics of interventions

- Antibiotic type, mode of administration, dose and interval
- 'Initially oral' or 'sequential intravenous to oral' study (see: 'Types of studies')
- Duration of therapy (median)

Characteristics of outcome measures

- Number of deaths at 30 days or during the study duration
- Mortality caused by the infectious episode

- Number of treatment failures (as defined)
- Number of treatment failures not due to addition of intravenous antibiotic for the primary infection
- Adverse reactions (causing death or permanent disability; requiring discontinuation; any other)
- Number of patients excluded after randomisation
- Lost to follow-up (dropouts) before the end of study

Assessment of risk of bias in included studies

Two review authors working independently assessed the trials fulfilling the review inclusion criteria for methodological quality. This was done using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), which are based on the evidence of a strong association between poor allocation concealment and overestimation of effect (Schulz 1995), as defined below.
A. Low risk of bias (adequate allocation concealment).
B. Moderate risk of bias (uncertainty regarding allocation concealment).
C. High risk of bias (inadequate allocation concealment).
In addition to the adequacy of allocation concealment, methods of allocation generation, blinding, intention-to-treat analysis, exclusions after randomisation, randomisation unit and publication status were recorded independently by the two review authors. Measures of quality were used for sensitivity analysis.

Assessment of heterogeneity

Heterogeneity (degree of difference between the results of different trials) in the results of the trials was initially graphically inspected and assessed by a test of heterogeneity (Chi^2 test and I^2 statistic). We had anticipated between-trial variation in estimation of morbidity and mortality for studies comparing broad-spectrum oral treatment versus narrow-spectrum treatment and for studies comparing patients at different risk levels. Heterogeneity was explored through stratifying the above defined patient subgroups (in the 'Objectives'), separating patients with low risk criteria (Table 1).

A funnel plot estimating the treatment effect against the precision of the trials (plots of the log of the relative risk for efficacy against the standard error) was examined in order to estimate potential asymmetry that may indicate selection bias (the selective publication of trials with positive findings) or methodological flaw in the small studies.

Data synthesis

Pooled risk ratios (RR) with 95% confidence intervals (CIs) were calculated for dichotomous data. Exclusions after randomisation were reported. A fixed-effect model (Mantel-Haenszel method) was used unless significant heterogeneity (P less than 0.10) was detected, in which case a random-effects model (DerSimonian and Laird method) was used.

Subgroup analyses were performed to investigate the effects of age (children versus adults), source of infection (unexplained fever versus documented infection), severity of neutropenia (absolute neutrophil count equal to or greater than 0.1 cells x 10^9/L versus absolute neutrophil count less than 0.1 cells x 10^9/L), and type of malignancy (solid tumour versus haematological malignancy).

RESULTS

Description of studies

Results of the search

Potentially relevant references were identified through the electronic databases. These references were screened for RCTs in cancer patients with neutropenia, fever and antibiotic regimens according to the protocol. Eighty trials were considered potentially eligible for this review, including six articles identified through references cited in the included studies and in major review articles in the field (Freifeld 1997; Hughes 2002; Kern 2001a; Klaassen 2000a; Paesmans 2000; Rolston 1999; Viscoli 2002).

Included studies

Twenty-two published RCTs were included in the review. Additionally two conference proceedings, identified through the ICAAC search, were included (Rolston 1995; Samonis 1997). Further information was provided by Dr Anaissie (Samonis 1997).

The studies were performed between the years 1989 and 2007, and included 965 randomised patients and an additional 2177 randomised episodes in 1407 patients. The age of the patients ranged from nine months to 85 years. Oral antibiotics were compared to intravenous antibiotics, both given empirically and as the initial empirical treatment ('initial oral') in 16 trials (Brack 2012*; Cagol 2009*; Cornely 2003; Freifeld 1999; Gupta 2009*; Hidalgo 1999; Innes 2003; Kern 1999; Malik 1992; Niho 2004; Petrilli 2000; Rolston 1995; Rubenstein 1993; Samonis 1997; Sebban 2009*; Velasco 1995). In the other five trials (Flaherty 1989; Giamarellou 2000; Mullen 1999; Paganini 2000; Paganini 2003; Shenep 2001) the patients randomised to 'oral treatment' received intravenous antibiotics prior to oral therapy ('sequential'). In two sequential trials (Flaherty 1989; Giamarellou 2000) the randomisation procedure was carried out at presentation but the patients were switched to oral therapy only 72 hours later.

Some exclusion criteria were similar among trials: haemodynamic instability, hypotension, altered mental status, respiratory failure, poor clinical condition, renal failure, abnormal liver function tests, no ability to swallow or take oral medication, allergy to study drugs, pregnancy and lactation. Additional case definitions varied between the trials despite the attempts of all trials to identify patients at low risk for mortality and complications (Table 2). Patients with haematological malignancy were excluded in three studies (Hidalgo 1999; Niho 2004; Samonis 1997). Patients with acute leukaemia were included in Brack 2012* (after maintenance treatment only); Freifeld 1999 (excluding patients with "neutropenia expected to last greater than 10 days"); Gupta 2009* (after maintenance treatment only); Giamarellou 2000; Malik 1992; Paganini 2003; Rolston 1995; Rubenstein 1993. Patients undergoing bone marrow or allogeneic stem cell transplantation were specifically excluded in eight trials (Brack 2012*; Cornely 2003; Freifeld 1999; Gupta 2009*; Innes 2003; Kern 1999; Mullen 1999; Paganini 2000).

Patients with any source of infection at presentation were included in six of the 'initial oral' trials (Cornely 2003; Malik 1992; Niho 2004; Petrilli 2000; Rubenstein 1993; Velasco 1995) and the 'sequential' studies. In the other studies patients with a specific source of infection were excluded: pneumonia was an exclusion criterion in six trials (Freifeld 1999; Hidalgo 1999; Innes 2003; Mullen 1999;

Samonis 1997; Shenep 2001); patients with infected intravascular catheters or tunnelitis were excluded in seven trials (Freifeld 1999; Innes 2003; Kern 1999; Mullen 1999; Paganini 2000; Paganini 2003; Shenep 2001); perirectal or severe cellulitis was an exclusion criterion in six trials (Hidalgo 1999; Innes 2003; Mullen 1999; Paganini 2000; Paganini 2003; Shenep 2001); Kern 1999 excluded known bacterial, viral or fungal infection; and Paganini 2000 excluded uncontrolled local infection. In one trial (Sebban 2009*) a MASCC score of 21 or lower was an inclusion criterion.

The oral antibiotics differed between trials: antipneumococcal quinolones in two trials (Paganini 2003; Sebban 2009*), other quinolones in 10 trials (Brack 2012*; Cagol 2009*; Flaherty 1989; Giamarellou 2000; Gupta 2009*; Hidalgo 1999; Malik 1992; Mullen 1999; Petrilli 2000). Quinolones were given in combination with ampicillin-clavulanate, ampicillin-sulbactam, or penicillin V in nine trials (Brack 2012*; Cagol 2009*; Freifeld 1999; Gupta 2009*; Innes 2003; Kern 1999; Niho 2004; Rolston 1995; Samonis 1997; Velasco 1995) and in combination with clindamycin in one trial (Rubenstein 1993). The antibiotics given orally were different in most studies from the drugs given intravenously.

The setting of therapy also varied. All patients were treated as outpatients in six trials (Cornely 2003; Gupta 2009*; Mullen 1999; Paganini 2003; Petrilli 2000; Rolston 1995; Rubenstein 1993). Patients randomised to oral therapy were treated as outpatients while the control group was treated in hospital in three trials (Hidalgo 1999; Innes 2003; Samonis 1997). Therapy was initiated in hospital and continued at home in two trials (Brack 2012*; Sebban 2009*). In the rest of the trials all patients were treated in hospital.

With both regimens few studies had high mortality rates (5% to 8.8%) (Flaherty 1989; Giamarellou 2000; Kern 1999; Malik 1992). This can be explained by the design of the trials: randomisation of patients not episodes (Giamarellou 2000; Kern 1999; Malik 1992), a longer follow-up period (Kern 1999), and not applying most low risk criteria for inclusion (Malik 1992).

Excluded studies

Fifty-eight trials were excluded from this review (Characteristics of excluded studies). Reasons for their exclusion were the following.

- Not randomised trials (Ammann 2004; Aquino 1997; Aquino 2000; Bash 1994; Berrahal 1996; Chamilos 2005; Cornelissen 1995; Gardembas-Pain 1991; Escalante 2004; Freifeld 2011; Horowitz 1996; Lau 1994; Malik 1994; Malik 1997; Montalar Salcedo1999; Marra 2000; Mustafa 1996; Nepokul'chitskaia; Paganini 2001b; Papadimitris 1999; Vallejo 1997; Wacker 1997).
- Sequential oral - intravenous antibiotics were used for all the patients in both trial arms (Paganini 2001a).
- No intravenous treatment arm (Malik 1995). All patients received oral antibiotics, and were randomised to outpatient versus inpatient therapy.
- Sequential oral antibiotic therapy was compared to no treatment (or placebo) (Klaassen 2000; Santolaya 1997).
- No oral treatment arm (IATCG-EORTC 1994; Kibbler 1987; Meunier 1991; Rapoport 1999; Santolaya 2004; Sato 2008).
- Review (Cometta 2004; Copper 2011; Freifeld 1997; Leverger 2004; Mullen 2001; Tamura 2005).
- One study (Minotti 1999) included all patients with fever post-chemotherapy, neutropenic and non-neutropenic, and did not report the outcomes of neutropenic patients separately.
- Prophylaxis (Timmers 2007).

Risk of bias in included studies

Adequate allocation concealment was reported in six trials (Brack 2012*; Cagol 2009*; Cornely 2003; Giamarellou 2000; Kern 1999; Sebban 2009*); information regarding adequate allocation concealment was provided by the contact authors in five other trials (Hidalgo 1999; Innes 2003; Paganini 2000; Shenep 2001; Velasco 1995). Two trials (Malik 1992; Niho 2004) reported how the allocation concealment was undertaken but its adequacy was unclear. These trials used sealed envelopes, however, no mention was made about whether the envelopes were opaque and the trials were assessed as at unclear risk of bias. There was no information regarding concealment of allocation in the other nine trials. Two trials were double blinded (Cagol 2009*; Freifeld 1999) and in one the outcomes assessors were blinded to the treatment arm (Kern 1999). Blinding was not specified in the other trials.

Duration of follow-up was predefined only in three trials (Cornely 2003; Kern 1999 (reported); Paganini 2000 (data from author)). In the other trials follow-up varied according to the length of the neutropenic febrile episode. In two trials (Giamarellou 2000; Innes 2003) the patients were followed for a predefined time after resolution of fever. In the other trials patients were followed until the end of the febrile neutropenic episode or until the end of antibiotic treatment.

Five per cent (median, range 0 to 0.18) of the patients were excluded from the final analysis. One trial provided no information about exclusions from the final analysis (Rolston 1995).

The unit of randomisation was the patient in four trials (Giamarellou 2000; Kern 1999; Malik 1992; Samonis 1997) and the episode of febrile neutropenia in the other trials. The later trials included 2050 episodes in 1407 patients; the number of patients included was not provided in three trial (Cornely 2003; Hidalgo 1999; Rolston 1995).

Graphical representation of the risk of bias is provided in Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

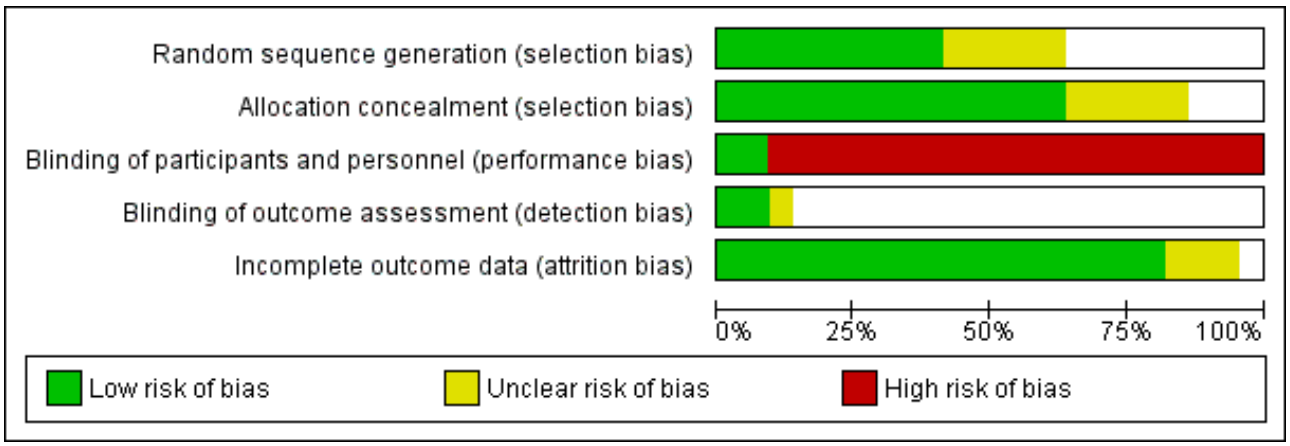


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

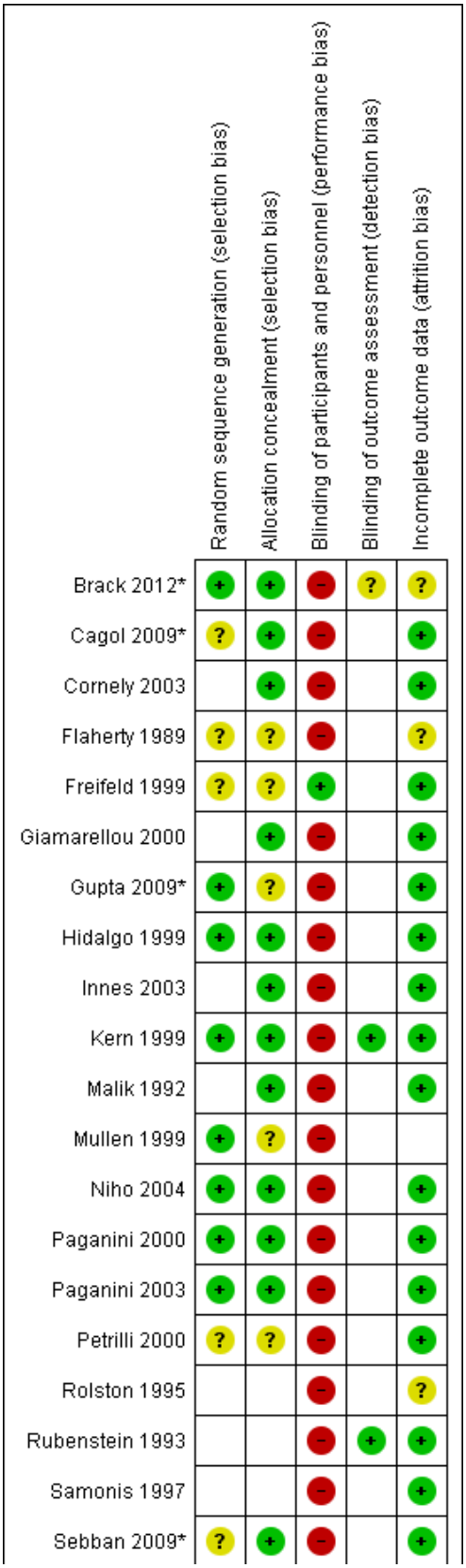
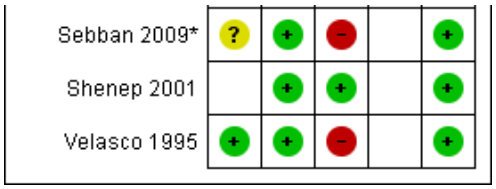


Figure 2. (Continued)



Effects of interventions

See: **Summary of findings for the main comparison** Oral compared to intravenous antibiotic therapy for febrile neutropenia in cancer patients

Mortality (9 trials, 1392 patients or episodes)

No difference in mortality (from any cause or caused by the infectious episode) between oral and intravenous treatment was demonstrated (RR 0.95, 95% CI 0.54 to 1.68, Analysis 1.1).

Treatment failure (all trials, 3135 patients or episodes)

There was no significant difference in failure rate between the two interventions (comparison 01, outcome 02, Analysis 1.2). The RR of treatment failure for 'initial oral' studies was 0.89 (95% CI 0.79 to 1.03, N = 2189), and 1.07 (95% CI 0.90 to 1.27, N = 946) for 'sequential' studies. A comparable RR was calculated for failure not due to modification of the initial regimen.

Per protocol analysis gave similar results to those of the ITT analysis (per protocol analysis: RR 0.98, 95% CI 0.86 to 1.11, all trials, 2912 patients, Analysis 1.3).

Adverse events

No deaths or permanent damage were attributed to the oral therapy in any of the trials. Adverse effects that required discontinuation of the assigned antibiotic therapy were reported in 15 (Flaherty 1989; Freifeld 1999; Giamarellou 2000; Hidalgo 1999; Innes 2003; Malik 1992; Mullen 1999; Niho 2004; Paganini 2000; Rubenstein 1993; Shenep 2001; Velasco 1995) (also Cornely 2003;Gupta 2009*; Kern 1999; Paganini 2003; Petrilli 2000), which reported side effects, of the 17 trials. Separate analysis of the 'initial oral' studies revealed significantly more adverse events requiring discontinuation among orally treated patients (RR 2.78, 95% CI 1.14 to 6.75, Analysis 1.4). This finding is consistent with the high rate of gastrointestinal adverse events with oral antibiotics as shown in Analysis 1.5, and with the fact that these events hamper any oral but not intravenous treatment (Cornely 2003; Freifeld 1999; Giamarellou 2000; Innes 2003; Kern 1999; Malik 1992; Niho 2004; Paganini 2000; Paganini 2003; Petrilli 2000; Rubenstein 1993; Shenep 2001; Velasco 1995) ('post-protocol' analysis).

Dropouts (lost to follow-up) before end of study

Nineteen trials reported the number of patients who were lost to follow-up before the end of the study in each group (Cornely 2003; Freifeld 1999; Giamarellou 2000; Hidalgo 1999; Innes 2003; Kern 1999; Malik 1992; Niho 2004; Paganini 2000; Paganini 2003; Petrilli 2000; Rubenstein 1993; Samonis 1997; Shenep 2001; Velasco 1995). No significant difference in the number of dropouts was found between the oral and intravenous (IV) treatment (RR 0.82, 95% CI 0.61 to 1.10, N = 2802).

Treatment failure - age

The outcomes of patients younger than 60 years of age versus older patients could not be extracted from the original publications.

There was no difference in the failure rates between the assigned treatments in the trials that included only children (RR 1.02, 95% CI 0.82 to 1.28, N = 1013, 8 trials) as well as in the trials in adults (RR 0.98, 95% CI 0.85 to 1.12, N = 1652, 12 trials, Analysis 2.1). One study (Kern 1999) included a low number of children and was considered for the purpose of the analysis as addressing an adult population. One death was documented among children (Brack 2012*) treated with intravenous antibiotics.

Treatment failure - source of infection

Treatment failure in relation to evidence of documented infection was addressed in trials (Freifeld 1999; Giamarellou 2000; Hidalgo 1999; Kern 1999; Malik 1992; Rolston 1995; Rubenstein 1993; Samonis 1997). There were no significant differences in treatment failure rate among the patients with unexplained fever (RR 1.03, 95% CI 0.79 to 1.33, N = 924) and those with documented infections (RR 1.00, 95% CI 0.84 to 1.19, N = 641, Analysis 2.2). In one trial (Freifeld 1999) the assessment was made at presentation while in the other trials assessment was done after 48 hours and therefore could not serve as a tool to assess the risk of patients ahead of treatment (unless switching to IV antibiotic treatment after 48 hours).

Treatment failure - severity of neutropenia

Failures according to the absolute neutrophil count (ANC) were analysed in three studies (Kern 1999; Rubenstein 1993; Shenep 2001).

No significant difference in treatment failure rate was found among patients with severe neutropenia (RR 1.07, 95% CI 0.76 to 1.49, N = 370). Among patients with ANC greater than 0.1 (10^9 cells/L) the risk of infection was not increaed with oral antibiotics (RR 0.66, 95% CI 0.45 to 0.98, N = 328, Analysis 2.3).

No deaths had occurred in patients with ANC greater than 0.1 (10^9 cells/L) at presentation.

Treatment failure - type of malignancy

Two trials (Hidalgo 1999; Samonis 1997) included only patients with solid tumours and patients with lymphoma. One trial (Petrilli 2000) included 96% patients and another trial (Cagol 2009*) included 90% of patients with solid tumours and were analysed as such; two trials (Rolston 1995; Rubenstein 1993) provided the failure rates of both oral and intravenous treatments among patients in accordance with the background malignancy; one trial had included only haematological cancer patients (Giamarellou 2000). No difference in treatment failure was demonstrated in patients

with solid tumours (RR 0.89, 95% CI 0.70 to 1.12, N = 990) and in patients with haematological malignancy (RR 1.04, 95% CI 0.84 to 1.28, N = 312, Analysis 2.4).

Comparison of mortality in subgroups could not be performed due to the low rate of deaths.

Continuous data

Due to insufficiently reported continuous outcome data, such as duration of fever, duration of antibiotic therapy, and length of hospital stay, these data could not be analysed.

Sensitivity and subgroup analyses

Sensitivity analyses of studies by the risk of bias (according to the adequacy of allocation concealment: low risk of bias, unclear; and according to blinding: blinding versus no blinding) showed no significant impact on the risk of treatment failure. Sensitivity analyses on different case definitions (trials including only patients with solid tumours versus trials including patients with solid and haematological malignancies; trials including patients with acute leukaemia versus trials excluding them; trials excluding patients with any identified source of infection at presentation versus trials including patients regardless of the source of infection; the above mentioned subgroups) showed similar RRs.

Treatment setting

Treatment setting (in or out of hospital) had no effect on the results (Analysis 4.1).

Antibiotics used in the trials

Quinolones alone were tested in nine (Cornely 2003; Flaherty 1989; Giamarellou 2000; Hidalgo 1999; Malik 1992; Mullen 1999; Paganini 2003; Petrilli 2000; Sebban 2009*) of the 22 trials in the pooled analysis. The dosage used varied from 400 to 800 mg of ofloxacin, and 600 to 2250 mg of ciprofloxacin daily, and in one trial 400 mg moxifloxacin daily. The quinolones were most commonly used with ampicillin-clavulanate at a maximal daily dosage of 1500 to 1875 mg. When analyses were performed according to oral antibiotic regimen, we observed no significant impact of quinolones treatment alone versus quinolones in combination with other antibiotics ('post-protocol' analysis, Analysis 4.2).

Funnel plot asymmetry

No significant heterogeneity was found in any of the outcomes evaluated (Figure 3, Figure 4).

Figure 3. Funnel plot of comparison: 1 Oral versus intravenous antibiotic therapy, outcome: 1.1 Mortality.

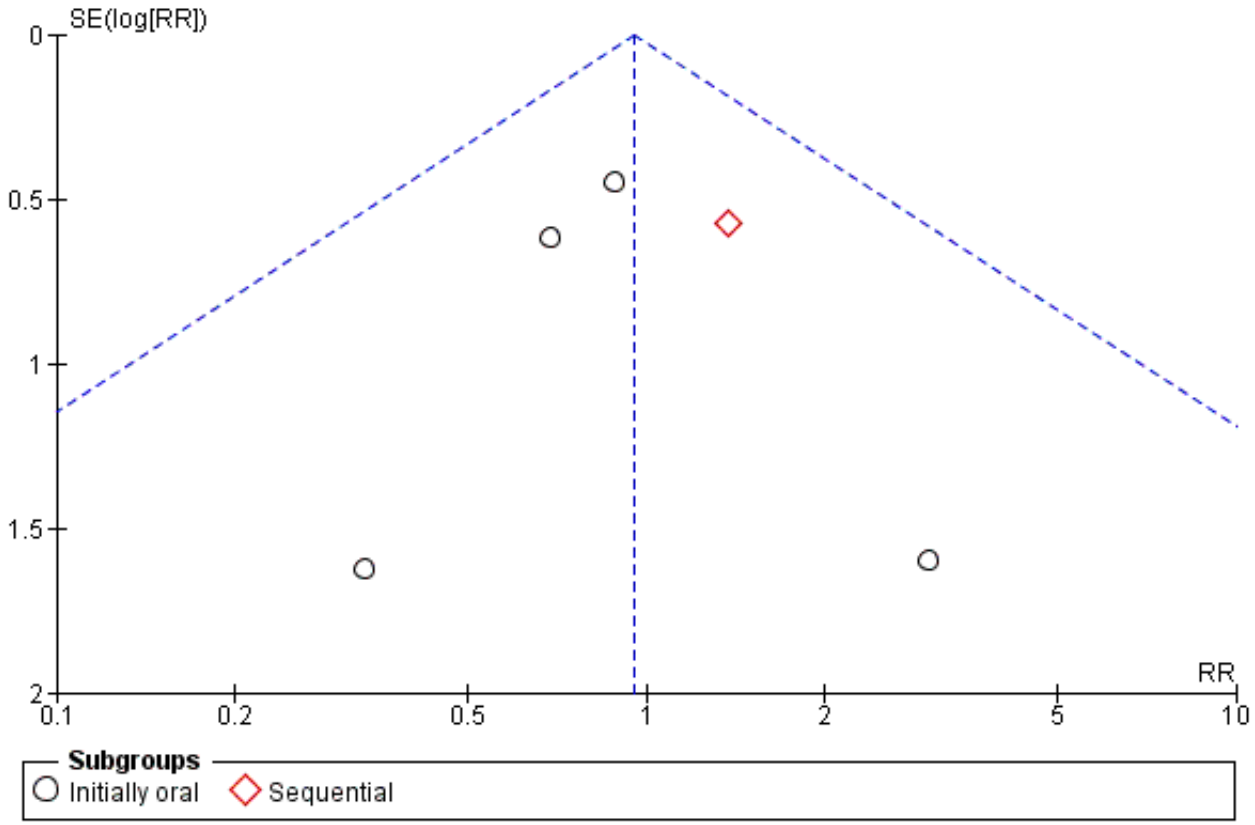
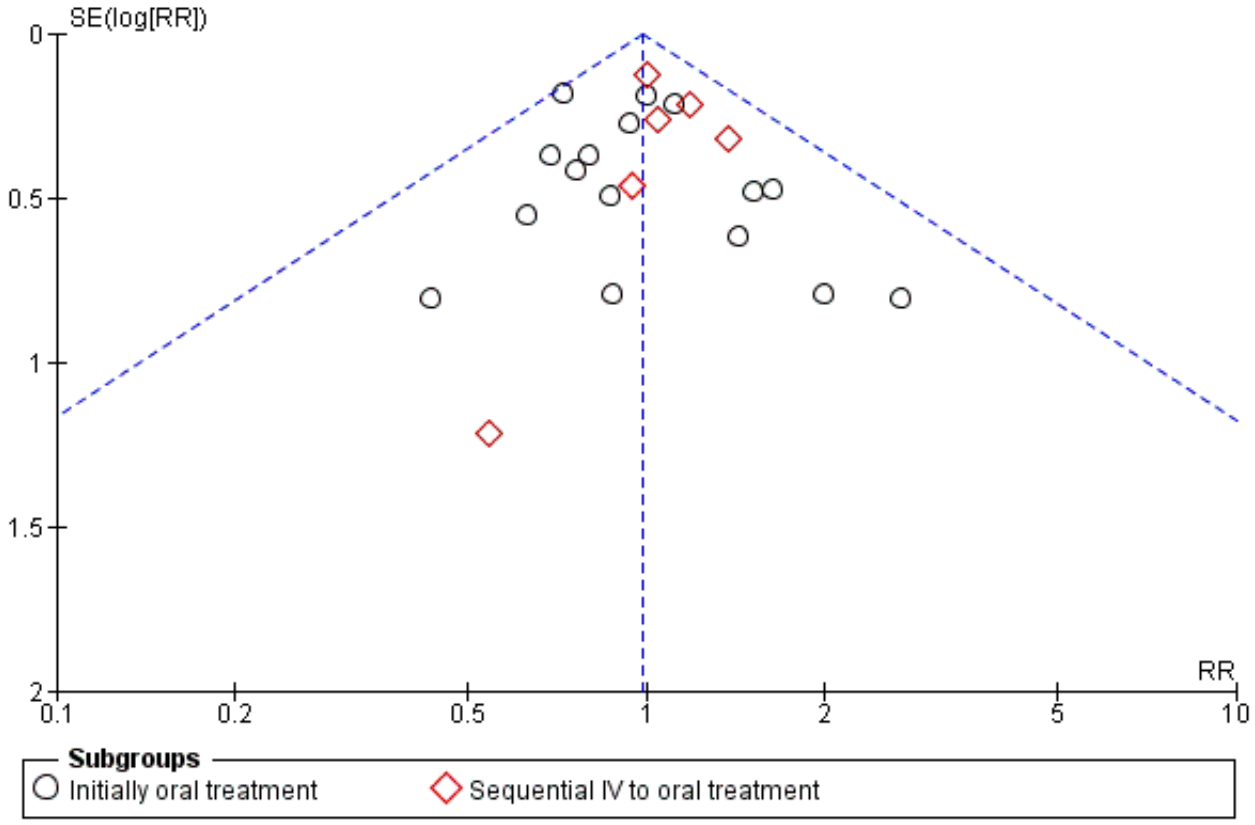


Figure 4. Funnel plot of comparison: 1 Oral versus intravenous antibiotic therapy, outcome: 1.3 Treatment failure - per protocol analysis.



DISCUSSION

The rates of treatment failure and mortality were not statistically significantly different in neutropenic patients given oral and intravenous antibiotic treatments. The RR for treatment failure in patients treated with oral antibiotics was 0.95. The RR for a fatal outcome was 0.95. No significant heterogeneity was shown for both comparisons. ITT analysis might favour equivalence, however the results of the per protocol analysis were similar to those of the primary analysis.

These effects were stable in a range of patient subgroups. The RR was similar across different case definitions of the underlying disease and the cause of fever. The RR did not depend on the age of the patients or on the antibiotic regimen. It was similar in studies that started patients on immediate oral treatment and in those that switched to oral treatment after a short time of intravenous treatment. Introduction of bias by inadequate randomisation or allocation concealment was shown to be unlikely by the sensitivity analysis. There was a trend toward more adverse effects in patients given oral treatment. However the majority were gastrointestinal complaints that did not necessitate discontinuation of therapy.

One limitation of the analysis is its inability to define the patients who may be offered oral antibiotics. This is due to the variations in the inclusion and exclusion criteria of the included trials. The difference in low risk criteria is not surprising, the concept of low risk neutropenic fever and its definition developed during the years in which the studies were performed. Different prognostic criteria evolved based on observational studies. An international collaboration had led to the development of a validated weighted scoring system identifying low risk patients, adopted by the Infectious Diseases Society of America (IDSA) (Chamilos 2005; Hughes 2002; Klastersky 2000; Klastersky 2006). Only one of the trials added in the current version (Sebban 2009*) incorporated that scoring system as an inclusion criterion.

Exclusion criteria that were common to all studies were criteria defining severe sepsis (mainly haemodynamic instability and organ failure: altered mental status, respiratory failure, renal and liver abnormalities), inability to swallow or take oral medication, allergy to study drugs, pregnancy and lactation. Most studies did not include patients with acute leukaemia and about half excluded patients with pneumonia, severe cellulitis or intravascular infection.

The low mortality rate led to wide CIs in the absolute risk reduction. To confirm equivalence of two treatments, we should ideally be able to show that any estimate of risk that is included within the CI lies within a predefined range of equivalence (as the CI of the effect of the recommended treatment) and has no clinical significance (Jones 1996). In a population with an expected mortality of less than 1% this uncertainty may have no real consequences.

For treatment failure the CI is narrower and probably has no clinical importance since failure means mainly a change in the antibiotic regimen.

AUTHORS' CONCLUSIONS

Implications for practice

Oral antibiotic therapy can be safely offered to febrile children and adults with neutropenia who are haemodynamically stable, have no organ failure, can take oral medications, do not have pneumonia, infection of a central line or a severe soft-tissue infection, and do not suffer from acute leukaemia. These criteria stand in close proximity to those of the IDSA guidelines for the treatment of neutropenic patients (Hughes 2002). Selection of candidates for oral therapy can also be based on the MASCC scoring system (Klastersky 2000).

The analysis offered no data in support of a specific oral regimen, but in light of the preponderance of Gram-positive infections (EORTC 1990; Hughes 2002; Kamana 2005) the combination of a quinolone and a second drug active against Gram-positive bacteria (for example ampicilin-clavulanate) seems prudent.

This review did not refer to the issue of home therapy. It could be assumed that home therapy can be offered to a similar population as that approved for oral treatment. In some of the included studies oral therapy was given on an ambulatory basis. The view is that patients can be treated in hospital or under close supervision on an ambulatory basis.

Implications for research

A future trial of oral versus intravenous antibiotic treatment should include febrile neutropenic patients with mild and stable sepsis, regardless of their underlying disorder, source of infection or neutrophil count. Its sample size should be based on considerations of equivalence (Jones 1996). The definitions of response and failure and the reported outcomes should be based on the guidelines on methodology for clinical trials involving patients with fever and neutropenia (Feld 1998; Feld 2000; Feld 2002).

For low risk patients (as defined by MASCC or the above criteria) different oral regimens should be compared. Using mortality as the primary outcome in such a trial might translate into a prohibitive sample size. However, the sample size of a trial needed to further reduce the CI shown in the present analysis might be smaller and manageable.

In addition, a randomised controlled trial comparing different oral antibiotic regimens in low risk patients with fever and neutropenia, and in particular fourth generation quinolones with activity against Gram-positive bacteria and anaerobes versus a previous generation quinolone plus ampicilin-clavulanate, is warranted.

ACKNOWLEDGEMENTS

We warmly thank Clare Jess and Gail Quinn, Managing Editors of the Cochrane Gynaecological Cancer Group, for there helpful editorial advice and assistance in obtaining manuscripts.

We thank Jane Hayes, Information Manager of the Cochrane Gynaecological Cancer Group for her support and help in bringing the review up-to-date.

We would like to express our appreciation to all the authors who responded to our letters and supplied additional information on their studies: Drs Ammann (Brack 2012*), Freifeld, Hidalgo, Niho, Paesmans (Kern 1999), Paganini, Shenep, Velasco, Marshall (Innes 2003) who supplied the full unpublished manuscript and Dr Anaissie for providing unpublished data from Samonis 1997. We would like to thank Mr Ochan Kilama from Bayer Italia for clarifying the details of Minotti 1999 though not included in the analysis.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group. The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Brack 2012* *{published data only}*

Brack E, Bodmer N, Simon A, Leibundgut K, Kühne T, Niggli FK, et al. First-day step-down to oral outpatient treatment versus continued standard treatment in children with cancer and low-risk fever in neutropenia. A randomized controlled trial within the multicenter SPOG 2003 FN study. *Pediatric Blood & Cancer* 2012;**59**(3):423-30.

Lüthi F, Leibundgut K, Niggli FK, Nadal D, Aebi C, Bodmer N, et al. Serious medical complications in children with cancer and fever in chemotherapy-induced neutropenia: results of the prospective multicenter SPOG 2003 FN study. *Pediatric Blood & Cancer* 2012;**59**(1):90-5.

Cagol 2009* *{published data only}*

* Cagol AR, Castro Junior CG, Martins MC, Machado AL, Ribeiro RC, Gregianin LJ, et al. Oral vs. intravenous empirical antimicrobial therapy in febrile neutropenic patients receiving childhood cancer chemotherapy. *Jornal de Pediatria* 2009;**85**(6):531-5.

Cornely 2003 *{published data only}*

Cornely OA, Wicke T, Seifert H, Bethe U, Schwonzen M, Reichert D, et al. Once-daily oral levofloxacin monotherapy versus piperacillin/tazobactam three times a day: a randomized controlled multicenter trial in patients with febrile neutropenia. *International Journal of Hematology* 2004;**79**(1):74-8. [MEDLINE: 14979482]

Flaherty 1989 *{published data only}*

Flaherty JP, Waitley D, Edlin B, George D, Arnow P, O'Keefe P, et al. Multicenter, randomized trial of ciprofloxacin plus azlocillin versus ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. *The American Journal of Medicine* 1989;**87 Suppl**:278-82.

Freifeld 1999 *{published data only}*

Freifeld A, Marchigiani D, Walsh T, Chanock S, Lewis L, Hiemenz J, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *The New England Journal of Medicine* 1999;**341**(5):305-11.

Giamarellou 2000 *{published data only}*

Giamarellou H, Bassaris HP, Petrikkos G, Busch W, Voulgarelis M, Antoniadou A, et al. Monotherapy with intravenous followed by oral high-dose ciprofloxacin versus combination therapy with ceftazidime plus amikacin as initial empiric therapy for granulocytopenic patients with fever. *Antimicrobial Agents and Chemotherapy* 2000;**44**:3264-71.

Gupta 2009* *{published data only}*

Gupta A, Swaroop C, Agarwala S, Pandey RM, Bakhshi S. Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia. *Journal of Pediatric Hematology/Oncology* 2009;**31**(9):635-41.

Hidalgo 1999 *{published and unpublished data}*

Hidalgo M, Hornedo J, Lumbreras C, Trigo JM, Colomer R, Perea S, et al. Outpatient therapy with oral ofloxacin for patients with low risk neutropenia and fever: a prospective, randomized clinical trial. *Cancer* 1999;**85**:213-9.

Innes 2003 *{published and unpublished data}*

* Innes HE, Smith DB, O'Reilly SM, Clark PI, Kelly V, Marshall E. Oral antibiotics with early hospital discharge compared with inpatient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. Data on file.

Kern 1999 *{published data only}*

Kern WV, Cometta A, De Bock R, Langenaeken J, Paesmans M, Gaya H. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *The New England Journal of Medicine* 1999;**341**:312-8.

Malik 1992 *{published data only}*

Malik IA, Abbas Z, Karim M. Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients. *Lancet* 1992;**339**:1092-6.

Mullen 1999 *{published data only}*

* Mullen CA, Petropoulos D, Roberts WM, Rytting M, Zipf T, Chan KW, et al. Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer* 1999;**86**:126-34.

Mullen CA, Petropoulos D, Roberts WM, et al. Economic and resource utilization analysis of outpatient management of fever and neutropenia in low-risk pediatric patients with cancer. *Journal of Pediatric Hematology/Oncology* 1999;**21**:212-8.

Niho 2004 *{published data only}*

* Niho S, Ohe Y, Goto K, H Ohmatsu, T Matsumoto, K Kubota, et al. Randomized trial of oral versus intravenous antibiotics in low-risk febrile neutropenic patients with lung cancer. *Japanese Journal of Clinical Oncology* 2004;**34**(2):69-73. [MEDLINE: 15067098]

Paganini 2000 *{published and unpublished data}*

Paganini HR, Sarkis CM, De Martino MG, Zubizarreta PA, Casimir L, Fernandez C, et al. Oral administration of cefixime to lower risk febrile neutropenic children with cancer. *Cancer* 2000;**88**:2848-52.

Paganini 2003 *{published data only}*

Paganini H, Gomez S, Ruvinsky S, Zubizarreta P, Latella A, Fraquelli L, et al. Outpatient, sequential, parenteral-oral antibiotic therapy for lower risk febrile neutropenia in children with malignant disease: a single-center, randomized, controlled trial in Argentina. *Cancer* 2003;**97**(7):1775–80. [MEDLINE: 12655535]

Petrilli 2000 *{published data only}*

Petrilli AS, Dantas LS, Campos MC, Tanaka C, Ginani VC, Seber A. Oral ciprofloxacin vs. intravenous ceftriaxone administered in an outpatient setting for fever and neutropenia in low-risk pediatric oncology patients: randomized prospective trial. *Medical and Pediatric Oncology* 2000;**34**:87-91.

Rolston 1995 *{published data only}*

Rolston K, Rubenstein E, Elting L, Escalante C, Manzullo E, Bodey GP. Ambulatory management of febrile episodes in low-risk neutropenic patients. Interscience conference on antimicrobial agents and chemotherapy. 1995:LM81.

Rubenstein 1993 *{published data only}*

Rubenstein EB, Rolston K, Benjamin RS, Loewy J, Escalante C, Manzullo E, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993;**71**:3640-6.

Samonis 1997 *{unpublished data only}*

Anaissie EJ, Samonis G, Kalbakis K, Georgoulias V. Therapy for low-risk cancer patients with fever and neutropenia: results of a prospective, randomized trial with cost analysis. Interscience conference on antimicrobial agents and chemotherapy. 1997:LM-51.

Sebban 2009* *{published data only}*

Sebban C, Dussart S, Fuhrmann C, Ghesquieres H, Rodrigues I, Geoffrois L, et al. Oral moxifloxacin or intravenous ceftriaxone for the treatment of low-risk neutropenic fever in cancer patients suitable for early hospital discharge. *Supportive Care in Cancer* 2008;**16**(9):1017-23.

Shenep 2001 *{published and unpublished data}*

Shenep JL, Flynn PM, Baker DK, Hetherington SV, Hudson MM, Hughes WT, et al. Oral cefixime is similar to continued intravenous antibiotics in the empirical treatment of febrile neutropenic children with cancer. *Clinical Infectious Disease* 2001;**32**:36-43.

Velasco 1995 *{published and unpublished data}*

Velasco E, Costa MA, Martins CA, Nucci M. Randomized trial comparing oral ciprofloxacin plus penicillin V with amikacin plus carbenicillin or ceftazidime for empirical treatment of febrile neutropenic cancer patients. *American Journal of Clinical Oncology-Cancer Clinical Trials* 1995;**18**(5):429-35.

References to studies excluded from this review

Ahmed 2007 *{published data only}*

Ahmed N, El-Mahallawy HA, Ahmed IA, Nassif S, El-Beshlawy A, El-Haddad A. Early hospital discharge versus continued hospitalization in febrile pediatric cancer patients with prolonged neutropenia: A randomized, prospective study. *Pediatric Blood & Cancer* 2007;**49**(6):786-92.

Ammann 2004 *{published data only}*

Ammann RA. Outpatient, sequential, parenteral-oral antibiotic therapy for lower risk febrile neutropenia in children with malignant disease: a single-center, randomized, controlled trial in Argentina. *Cancer* 2004;**100**(7):1547; author reply 1547-8.

Aquino 1997 *{published data only}*

Aquino VM, Buchanan GR, Tkaczewski I, Mustafa MM. Safety of early hospital discharge of selected febrile children and adolescents with cancer with prolonged neutropenia. *Medical and Pediatric Oncology* 1997;**28**:191-5.

Aquino 2000 *{published data only}*

Aquino VM, Herrera L, Sandler ES, Buchanan GR. Feasibility of oral ciprofloxacin for the outpatient management of febrile neutropenia in selected children with cancer. *Cancer* 2000;**88**:1710-4.

Bash 1994 *{published data only}*

Bash RO, Katz JA, Cash JV, Buchanan GR. Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. *Cancer* 1994;**74**(1):189-96.

Berrahal 1996 *{published data only}*

Berrahal F, Baume D, Burtey S, Mazzerbo F, Zanlucca S, Demichelis C. A study of intravenous ticarcillin/clavulanic acid and oral ciprofloxacin in the treatment of febrile neutropenic patients. *Journal de Pharmacie Clinique* 1996;**15**(Special issue):74-7.

Chamilos 2005 *{published data only}*

Chamilos G, Bamias A, Efstathiou E, Zorzou PM, Kastritis E, Kostis E, et al. Outpatient treatment of low-risk neutropenic fever in cancer patients using oral moxifloxacin. *Cancer* 2005;**103**(12):2629-35. [MEDLINE: 15856427]

Chernobelski *{published data only}*

Chernobelski P, Lavrenkov K, Rimar D, Riesenberg K, Schlaeffer F, Ariad S, et al. Prospective study of empiric monotherapy with ceftazidime for low-risk grade IV febrile neutropenia after cytotoxic chemotherapy in cancer patients. *Chemotherapy* 2006;**52**(4):185-9.

Cometta 2004 *{published data only}*

Cometta A, Kern W. [Treatment with oral antibiotics of febrile neutropenia in onco-haematology. The experience of the EORTC antimicrobial group]. *Presse Medicale* 2004;**33**(5):327-9.

Copper 2011 *{published data only}*

Cooper MR. Durand CR. Beaulac MT. Steinberg M. Single-agent, broad-spectrum fluoroquinolones for the outpatient treatment of low-risk febrile neutropenia. *Annals of Pharmacotherapy* 2011;**45**(9):1094-102.

Cornelissen 1995 *{published data only}*

Cornelissen JJ, Rozenberg-Arska M, Dekker AW. Discontinuation of intravenous antibiotic therapy during persistent neutropenia in patients receiving prophylaxis with oral ciprofloxacin. *Clinical Infectious Diseases* 1995;**21**:1300-2.

Dommett 2009 *{published data only}*

Dommett R, Geary J, Freeman S, Hartley J, Sharland M, Davidson A, et al. Successful introduction and audit of a

step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. *European Journal of Cancer* 2009;**45**(16):2843-9.

Escalante 2004 *{published data only}*

Escalante CP, Weiser MA, Manzullo E, Benjamin R, Rivera E, Lam T, et al. Outcomes of treatment pathways in outpatient treatment of low risk febrile neutropenic cancer patients. *Supportive Care in Cancer* 2004;**12**(9):657-62.

Flores 2010 *{published data only}*

Flores IQ, Ershler W. Managing neutropenia in older patients with cancer receiving chemotherapy in a community setting. *Clinical Journal of Oncology Nursing* 2010;**14**(1):81-6.

Freifeld 1997 *{published data only}*

Freifeld A, Pizzo P. Use of fluoroquinolones for empirical management of febrile neutropenia in pediatric cancer patients. *The Pediatric Infectious Disease Journal* 1997;**16**:140-5; discussion 145-6, 160-2.

Freifeld 2008 *{published data only}*

Freifeld A, Sankaranarayanan J, Ullrich F, Sun J. Clinical practice patterns of managing low-risk adult febrile neutropenia during cancer chemotherapy in the USA. *Supportive Care in Cancer* 2008;**16**(2):181-91.

Freifeld 2011 *{published data only}*

Freifeld AG, Sepkowitz KA. No place like home? Outpatient management of patients with febrile neutropenia and low risk. *Journal of Clinical Oncology* 2011;**20**(30):3952-4.

Gardembas-Pain 1991 *{published data only}*

Gardembas-Pain M, Desablens B, Sensebe L, Lamy T, Ghandour C, Boasson M. Home treatment of febrile neutropenia: an empirical oral antibiotic regimen. *Annals of Oncology* 1991;**2**:485-7.

Guyotat 1985 *{published data only}*

Guyotat D, Plonton C, Fiere D. A randomized trial of oral vancomycin in neutropenic patients. *Progress in Clinical and Biological Research* 1985;**181**:263-5.

Hendricks 2011 *{published data only}*

Hendricks AM, Loggers ET, Talcott JA. Costs of home versus inpatient treatment for fever and neutropenia: analysis of a multicenter randomized trial. *Journal of Clinical Oncology* 2011;**29**(30):3984-9.

Horowitz 1996 *{published data only}*

Horowitz HW, Holmgren D, Seiter K. Stepdown single agent antibiotic therapy for the management of the high risk neutropenic adult with hematologic malignancies. *Leukemia and Lymphoma* 1996;**23**(1-2):159-63.

IATCG-EORTC 1994 *{published data only}*

International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Reduction of fever and streptococcal bacteremia in granulocytopenic patients with cancer. A trial of oral penicillin V or placebo combined with pefloxacin. *JAMA* 1994;**272**:1183-9.

Kamana 2005 *{published data only}*

Kamana M, Escalante C, Mullen CA, Frisbee-Hume S, Rolston KV. Bacterial infections in low-risk, febrile neutropenic patients. *Cancer* 2005;**104**(2):422-6.

Kern 2006 *{published data only}*

Kern W. Risk assessment and treatment of low-risk patients with febrile neutropenia. *Clinical Infectious Diseases* 2006;**42**(4):533-40.

Kibbler 1987 *{unpublished data only}*

* Kibbler CC, Pomroy L, Sage RJ, Mannan P, Noone P, Prentice HG. The use of ciprofloxacin in the treatment of febrile neutropenic patients. Proceedings of the 33rd European Congress of Clinical Microbiology. 1987 11-14 May.

Klaassen 2000 *{published data only}*

Klaassen RJ, Allen U, Doyle JJ. Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. *Journal of Pediatric Hematology/Oncology* 2000;**22**:405-11.

Klastersky 2006 *{published data only}*

Klastersky J, Paesmans M, Georgala A, Muanza F, Plehiers B, Dubreucq L, et al. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *Journal of Clinical Oncology* 2006;**24**(25):4129-34.

Lau 1994 *{published data only}*

Lau RC, Doyle JJ, Freedman MH, King SM, Richardson SE. Early discharge of pediatric febrile neutropenic cancer patients by substitution of oral for intravenous antibiotics. *Journal of Pediatric Hematology/Oncology* 1994;**11**:417-21.

Leverger 2004 *{published data only}*

Leverger G. [Outpatient antibiotherapy in children with neutropenia and fever. A review of the literature.]. *Presse Medicale* 2004;**33**(5):330-7.

Luthi 2012 *{published data only}*

Lüthi F, Leibundgut K, Niggli FK, Nadal D, Aebi C, Bodmer N, et al. Serious medical complications in children with cancer and fever in chemotherapy-induced neutropenia: results of the prospective multicenter SPOG 2003 FN study. *Pediatric Blood & Cancer* 2012;**59**(1):90-5.

Malik 1994 *{published data only}*

Malik IA, Khan WA, Aziz Z, Karim M. Self-administered antibiotic therapy for chemotherapy-induced, low-risk febrile neutropenia in patients with nonhematologic neoplasms. *Clinical Infectious Diseases* 1994;**19**:522-7.

Malik 1995 *{published data only}*

Malik IA, Aziz Z, Khan WA. A randomized trial to evaluate the role of ofloxacin in the out-patient management of neutropenic febrile patients. *Annals of Oncology* 1992;**3 Suppl**:197.

* Malik IA, Khan WA, Karim M, Aziz Z, Khan MA. Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: results of a prospective randomized trial. *The American Journal of Medicine* 1995;**98**:224-31.

Malik 1997 *{published data only}*

Malik IA. Out-patient management of febrile neutropenia in indigent paediatric patients. *Annals of the Academy of Medicine, Singapore* 1997;**26**:742-6.

Marra 2000 *{published data only}*

Marra CA, Frighetto L, Quaia CB, et al. A new ciprofloxacin stepdown program in the treatment of high-risk febrile neutropenia: a clinical and economic analysis. *Pharmacotherapy* 2000;**20**:931-40.

Meunier 1991 *{published data only}*

Meunier F, Zinner SH, Gaya H, Calandra T, Viscoli C, Klastersky J, et al. Prospective randomized evaluation of ciprofloxacin versus piperacillin plus amikacin for empiric antibiotic therapy of febrile granulocytopenic cancer patients with lymphomas and solid tumors. The European Organization for Research on Treatment of Cancer International Antimicrobial Therapy Cooperative Group. *Antimicrobial Agents and Chemotherapy* 1991;**35**(5):873-8.

Minotti 1999 *{published data only}*

Minotti V, Gentile G, Bucaneve G, Iori AP, Micozzi A, Cavicchi F, et al. Domiciliary treatment of febrile episodes in cancer patients: a prospective randomized trial comparing oral versus parenteral empirical antibiotic treatment. *Supportive Care in Cancer* 1999;**7**:134-9.

Montalar Salcedo1999 *{published data only}*

Montalar Salcedo J, Oltra Ferrando A, Segura Huerta A, Santaballa Bertran A, Yuste Izquierdo A, Aparicio Urtasun J. Ofloxacin as monotherapy in the treatment of neutropenic fever. *Oncologia* 1999;**22**(8):42-7.

Mullen 2001 *{published data only}*

Mullen CA. Which children with fever and neutropenia can be safely treated as outpatients?. *British Journal of Haematology* 2001;**112**:832-7.

Mustafa 1996 *{published data only}*

Mustafa MM, Aquino VM, Pappo A, Tkaczewski I, Buchanan GR. A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. *The Journal of Pediatrics* 1996;**128**(6):847-9.

Nepokul'chitskaia *{published data only}*

Nepokul'chitskaia NV, Timakov AM, Kondratchik KL, Makhortykh T, Tarasova IS, Erina TA. [Cephalosporins in the treatment of children with oncohematologic diseases]. *Antibiotiki i Khimioterapiia (Moskva)* 1998;**43**:30-2.

Paganini 2001a *{published data only}*

Paganini H, Rodriguez-Brieshcke T, Zubizarreta P, Latella A, Firpo V, Casimir L, et al. Oral ciprofloxacin in the management of children with cancer with lower risk febrile neutropenia. *Cancer* 2001;**91**:1563-7.

Paganini 2001b *{published data only}*

Paganini H, Rodriguez-Brieshcke TR, Zubizarreta P, Latella A, Firpo V, Fernandez C. Validation of lower risk mortality profile in pediatric febrile neutropenia during cancer chemotherapy. *Medicina* 2001;**61**(1):63-6.

Papadimitris 1999 *{published data only}*

Papadimitris C, Dimopoulos MA, Kostis E, Papadimitriou C, Anagnostopoulos A, Alexopoulos G, et al. Outpatient treatment of neutropenic fever with oral antibiotics and granulocyte colony-stimulating factor. *Oncology* 1999;**57**:127-30.

Petrilli 2007 *{published data only}*

Petrilli A, Altruda Carlesse F, Alberto Pires Pereira C. Oral gatifloxacin in the outpatient treatment of children with cancer fever and neutropenia. *Pediatric Blood & Cancer* 2007;**49**(5):682-6.

Quezada 2007 *{published data only}*

Quezada G, Sunderland T, Chan KW, Rolston K, Mullen CA. Medical and non-medical barriers to outpatient treatment of fever and neutropenia in children with cancer. *Pediatric Blood & Cancer* 2007;**48**(3):273-7.

Rapoport 1999 *{published data only}*

Rapoport BL, Sussmann O, Herrera MV, Schlaeffer F, Otero JC, Pavlovsky S, et al. Ceftriaxone plus once daily aminoglycoside with filgrastim for treatment of febrile neutropenia: early hospital discharge versus standard in-patient care. *Chemotherapy* 1999;**45**(6):466-76.

Rolston 2006 *{published data only}*

Rolston KV, Manzullo EF, Elting LS, Frisbee-Hume SE, McMahon L, Theriault RL, et al. Once daily, oral, outpatient quinolone monotherapy for low-risk cancer patients with fever and neutropenia: a pilot study of 40 patients based on validated risk-prediction rules. *Cancer* 2006;**106**(11):2489-94.

Rolston 2010 *{published data only}*

Rolston KVI, Frisbee-Hume SE, Patel S, Manzullo EF, Benjamin RS. Oral moxifloxacin for outpatient treatment of low-risk, febrile neutropenic patients. *Supportive Care in Cancer* 2010;**18**(1):89-94.

Santolaya 1997 *{published data only}*

Santolaya ME, Villarroel M, Avendano LF, Cofre J. Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. *Clinical Infectious Diseases* 1997;**25**(1):92-7.

Santolaya 2004 *{published data only}*

Santolaya ME, Alvarez AM, Aviles CL, Becker A, Cofre J, Cumsille MA, et al. Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. *Journal of Clinical Oncology* 2004;**22**(18):3784-9.

Sato 2008 *{published data only}*

Sato T, Kobayashi R, Yasuda K, Kaneda M, Iguchi A, Kobayashi K. A prospective, randomized study comparing cefozopran with piperacillin-tazobactam plus ceftazidime as empirical therapy for febrile neutropenia in children with hematological disorders. *Pediatric Blood & Cancer* 2008;**51**(6):774-7.

Slavin 2007 *{published data only}*

Slavin MA, Grigg AP, Schwarer AP, Szer J, Spencer A, Sainani A, et al. A randomized comparison of empiric or pre-emptive antibiotic therapy after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2007;**40**(2):157-63.

Talcott 2011 *{published data only}*

Talcott JA, Yeap BY, Clark JA, Siegel RD, Loggers ET, Lu C, et al. Safety of early discharge for low-risk patients with febrile neutropenia: a multicenter randomized controlled trial. *Journal of Clinical Oncology* 2011;**29**(30):3977-83.

Tamura 2005 *{published data only}*

Tamura K. Clinical guidelines for the management of neutropenic patients with unexplained fever in Japan: validation by the Japan Febrile Neutropenia Study Group. *International Journal of Antimicrobial Agents* 2005;**26 Suppl 2**:S123-7; discussion S133-40.

Timmers 2007 *{published data only}*

Timmers GJ, Simoons-Smit AM, Leidekker ME, Janssen JJ, Vandenbroucke-Grauls CM, Huijgens PC. Levofloxacin vs. ciprofloxacin plus phenethicillin for the prevention of bacterial infections in patients with haematological malignancies. *Clinical Microbiology and Infection* 2007;**13**(5):497-503.

Uzun 1999 *{published data only}*

Uzun O, Anaissie EJ. Outpatient therapy for febrile neutropenia: who, when, and how?. *Journal of Antimicrobial Chemotherapy* 1999;**43**(3):317-20.

Vallejo 1997 *{published data only}*

Vallejo C, Caballero MD, Garcia-Sanz R, Hernandez JM, Vazquez L, Canizo MC, et al. Sequential intravenous-oral ciprofloxacin plus amoxycillin/clavulanic acid shortens hospital stay in infected non severe neutropenic patients. *Hematology & Cell Therapy* 1997;**39**(5):223-7.

Wacker 1997 *{published data only}*

Wacker P, Halperin DS, Wyss M, Humbert J. Early hospital discharge of children with fever and neutropenia: a prospective study. *Journal of Pediatric Hematology/Oncology* 1997;**19**(3):208-11.

Additional references

Bodey 1966

Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Annals of Internal Medicine* 1966;**64**(2):328-40.

Consensus panel 1990

From the Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. *Journal of Infectious Diseases* 1990;**161**(3):397-401.

EORTC 1990

EORTC International Antimicrobial Therapy Cooperative Group. Gram-positive bacteraemia in granulocytopenic cancer patients. *European Journal of Cancer* 1990;**26**(5):569-74.

Feld 1998

Feld R. Criteria for response in patients in clinical trials of empiric antibiotic regimens for febrile neutropenia. Is there agreement?. *Supportive Care in Cancer* 1998;**6**(5):444-8.

Feld 2000

Feld R. Multinational cooperation in trials and guidelines dealing with febrile neutropenia. *International Journal of Antimicrobial Agents* 2000;**16**(2):185-7.

Feld 2002

Feld R, Paesmans M, Freifeld AG, Klastersky J, Pizzo PA, Rolston KV, et al. Methodology for clinical trials involving patients with cancer who have febrile neutropenia: updated guidelines of the Immunocompromised Host Society/ Multinational Association for Supportive Care in Cancer, with emphasis on outpatient studies. *Clinical Infectious Diseases* 2002;**35**(12):1463-8.

Hann 1997

Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *British Journal of Haematology* 1997;**99**(3):580-8.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Oxford: Update Software, updated quarterly.

Hughes 2002

Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clinical Infectious Diseases* 2002;**34**(6):730-51.

Jones 1996

Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996;**313**(7048):36-9.

Kern 2001a

Kern WV. Risk assessment and risk-based therapeutic strategies in febrile neutropenia. *Current Opinion in Infectious Diseases* 2001;**14**(4):415-22.

Klaassen 2000a

Klaassen RJ, Goodman TR, Pham B, Doyle JJ. "Low-risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. *Journal of Clinical Oncology* 2000;**18**(5):1012-9.

Klastersky 2000

Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The multinational association for supportive care in cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *Journal of Clinical Oncology* 2000;**18**(16):3038-51.

Lucas 1996

Lucas KG, Brown AE, Armstrong D, Chapman D, Heller G. The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer* 1996;**77**(4):791-8.

Paesmans 2000

Paesmans M. Risk factors assessment in febrile neutropenia. *International Journal of Antimicrobial Agents* 2000;**16**(2):107-11.

Pizzo 1982

Pizzo PA, Robichaud KJ, Wesley R, Commers JR. Fever in the pediatric and young adult patients with cancer. A prospective study of 1001 episodes. *Medicine (Baltimore)* 1982;**61**(3):153-65.

Rackoff 1996

Rackoff WR, Gonin R, Robinson C, Kreissman SG, Breitfeld PB. Predicting the risk of bacteremia in childen with fever and neutropenia. *Journal of Clinical Oncology* 1996;**14**(3):919-24.

Rolston 1999

Rolston KV. New trends in patient management: risk-based therapy for febrile patients with neutropenia. *Clinical infectious diseases* 1999;**29**(3):515-21.

Schimpff 1971

Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *The New England Journal of Medicine* 1971;**284**(19):1061-5.

Schimpff 1986

Schimpff S. Empiric antibiotic therapy for granulocytopenic cancer patients. *The American Journal of Medicine* 1986;**80**(5C):13-20.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. *JAMA* 1995;**273**(5):408-12.

Talcott 1988

Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. *Archives of Internal Medicine* 1988;**148**(12):2561-8.

Talcott 1992

Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *Journal of Clinical Oncology* 1992;**10**(2):316-22.

Talcott 1994

Talcott JA, Whalen A, Clark J, Rieker PP, Finberg R. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. *Journal of Clinical Oncology* 1994;**12**(1):107-14.

Viscoli 2002

Viscoli C. Management of infection in cancer patients. Studies of the EORTC International Antimicrobial Therapy Group (IATG). *European Journal of Cancer* 2002;**38 Suppl 4**:S82-7.

References to other published versions of this review

Vidal 2004

Vidal L, Paul M, Ben dor I, Soares-Weiser K, Leibovici L. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients: a systematic review and meta-analysis of randomized trials. *Journal of Antimicrobial Chemotherapy* 2004;**54**(1):29-37.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brack 2012*

Methods	Randomisation: list of random numbers Allocation concealment: a set of numbered, sealed randomisation envelopes Blinding: no Exclusions from analysis: 7/69 episodes were excluded. 6 episodes due to protocol violation their allocation was not specified, 1 due to hypersensitivity/adverse event, 1 lost to follow-up
Participants	62 episodes in 52 patients, during 2004 to 2007, in Switzerland and Germany Type of malignancy: 50% solid tumour, 50% acute lymphoblastic leukaemia (not during induction)
Interventions	Sequential

Brack 2012* *(Continued)*

	Oral: ciprofloxacin (25–30 mg/kg/day, top dose 1500 mg/day, given in 2 daily doses) plus amoxicillin (65–80 mg/kg/day, top dose 2250 mg/day, given in 2 daily doses) IV: intravenous antimicrobial therapy
Outcomes	All cause mortality Treatment failure Length of therapy, and hospitalisation Adverse events
Notes	Early termination of the trial "Because of insufficient accrual, the study was closed early, before reaching the number of 90 randomized low-risk FN episodes of the first interim monitoring" Power calculation: as for a non-inferiority study: "Both efficacy and safety of experimental treatment were tested for non-inferiority compared to standard treatment using an unconditional exact non-inferiority test for binomial difference based on the standardized (score) test statistic [26– 28]. The 95% upper confidence bound (UCB) corresponding to this one-sided test was calculated. The acceptable non-inferiority margins of difference were set at 3.5% for safety and 10% for efficacy"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"list of random numbers"
Allocation concealment (selection bias)	Low risk	"At randomization, one of a set of numbered, sealed randomization envelopes containing the randomization allocation was opened by the treating oncologist"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding procedure
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/69 episodes were excluded. 6 episodes due to protocol violation their allocation was not specified , 1 due to hypersensitivity/adverse event, 1 lost to follow-up

Cagol 2009*

Methods	Randomisation: not reported Allocation concealment: adequate Blinding: no Exclusions from analysis: 0 episodes
Participants	episodes, 2002-2005, Brazil
Interventions	Oral ciprofloxacin amoxycillin-clavulanate IV: cefepime

Cagol 2009* *(Continued)*

Outcomes	Successful versus unsuccessful: unsuccessful if one or more of the following conditions indicative of invasive bacterial infection was observed: 1) haemodynamic instability unrelated to lost volume; 2) fever that had not abated 72 hours after starting antibiotics; 3) repeat episode of fever lasting at least 24 hours and occurring after the 48-hour period with no fever; 4) death during infection; 5) grade III and IV vomiting; and 6) infections that demanded the addition of antibiotics not included in the study protocol Adverse events
Notes	Early termination of the trial: no Power calculation: not as a non-inferiority study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"Randomization consisted of distributing patients into blocks of 10, with selection made by a pharmacist who drew lots before patients were recruited. Patients were allocated to either group A or group B, where patients in group A were given oral antimicrobial treatment and those in group B were given intravenous treatment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised episodes were included in analysis

Cornely 2003

Methods	Randomisation: not reported Allocation concealment: by phone Blinding: no Exclusions from analysis: 0 episodes Follow-up period: 30 days
Participants	34 episodes, during 2000-2002, Germany Age: range 20-77 yrs Type of malignancy: 38% solid tumour
Interventions	Initial oral Oral: levofloxacin 500 mg q 24h IV: tazocin 4.5 g q8h
Outcomes	All cause mortality Treatment failure Adverse events (any)
Notes	Randomisation of episodes

Cornely 2003 *(Continued)*

	Definitions of outcomes: Failure: no success, no fever 72h after randomisation with at least 7 subsequent afebrile days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	By phone
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised episodes/patients were analysed

Flaherty 1989

Methods	Randomisation: no information Allocation concealment: no information Blinding: no information Intention to treat: no Exclusions from analysis: 7/86 episodes, of unknown treatment assignment Follow-up period: end of fever and neutropenia
Participants	USA, 1988-1989 86 episodes of fever and neutropenia in 77 cancer patients Age: range 29-82 yrs Type of malignancy: acute leukaemia (30%), chronic leukemia (22%), lymphoma (6%), solid tumour (35%)
Interventions	Sequential Oral: ciprofluoxacin 300mg q12h + azlocillin 4g q6h for at least 72 hours, if favourable response change to oral ciprofluoxacin 750mg q12h as inpatients Oral2: ceftazidime 2g q8h +amikacin 7.5mg/kg q12h for at least 72 hours, if favourable response change to ciprofluoxacin 750 mg q12h as inpatients IV: ceftazidime 2g q8h +amikacin 7.5mg/kg q12h as inpatients
Outcomes	All cause mortality Treatment failure Number of patients who become afebrile Length of febrile episode Duration of therapy Adverse events (requiring discontinuation)
Notes	Journal publication Definitions of outcomes: Failure: any death prior to neutrophil recovery; addition of antibiotics (success with modification)

Risk of bias

Bias	Authors' judgement	Support for judgement

Flaherty 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/86 episodes, of unknown treatment assignment

Freifeld 1999

Methods	Randomisation: no information Allocation concealment: no information Blinding: double blind Intention to treat: no Exclusions from analysis: 52/284 episodes Follow-up period: end of fever and neutropenia
Participants	USA, 1992-1997 284 episodes of fever and neutropenia in 211 cancer patients Age: range 5-74 yrs Type of malignancy: leukemia or lymphoma (27%), solid tumour (73%)
Interventions	Initial oral Oral: ciprofluoxacin 10 mg/kg max 750mg q8h+ Augmentin 40 mg/kg/3 max 500mg q8h as inpatients IV: ceftazidime 30mg/kg max 2g q8h as inpatients
Outcomes	All cause mortality Treatment failure Treatment failure not due to modification of the primary intervention Lost to follow-up Adverse events (any, requiring discontinuation)
Notes	Journal publication Outcomes in subgroups: documented infections, severe neutropenia Definitions of outcomes: Failure: death or modification of antibiotic regimen. Reasons for modification: infection that was presumed to be inadeqautely treated; intolerance to oral medication; haemodynamic instability; progressive or breakthrough 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

Freifeld 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Giamarellou 2000

Methods	Randomisation: no information Allocation concealment: central Blinding: no Intention to treat: no Exclusions from analysis: 17/263 patients Follow-up period: 7 days following end of antibiotic treatment
Participants	Greece, 1992-1995 263 cancer patients with fever and neutropenia Age >18 years All had haematologic malignancies or aplastic anaemia
Interventions	Sequential Oral: ciprofluoxacin 400mg q8h for 72 hours, if responding change to oral ciprofluoxacin 750mg q12h as inpatients IV: ceftazidime 2g q8h +amikacin 500mg q12h as inpatients
Outcomes	All cause mortality infection-related mortality Duration of therapy Adverse events (any, requiring discontinuation)
Notes	Journal publication Outcomes in subgroups: FUO, haematological malignancy Definitions of outcomes: Failure: death due to infection, fever and/or pathogen did not respond nessasating a modification in the assigned regimen, clinical or microbiological relapse within 7 days after discontinuation, superinfection

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Central
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Gupta 2009*

Methods	Randomisation: "computer spreadsheet program" Allocation concealment: not reported Blinding: no Intention to treat: no Exclusions from analysis: 3/123 episodes
Participants	123 episodes in 88 patients, 2006-2007, India Age: the median age was 8.25 years (oral) and 7.75 years (intravenous) Type of malignancy: most frequent: acute lymphoblastic leukaemia in maintenance phase of therapy (33%), primitive neuro-ectodermal tumour (21%) and rhabdomyosarcoma (20%)
Interventions	Oral: ofloxacin 7.5mg/kg/dose every 12 hours + amoxycillin-clavulanate 12.5mg/kg (amoxycillin) every 8 hours IV: ceftriaxone 75 mg/kg/day + amikacin 15 mg/kg once daily
Outcomes	Treatment success (primary outcome variable) was defined as resolution of the febrile episode and neutropenia without change of regimen or hospitalisation. Non-resolution of fever or any other serious medical complications (with or without resolution of fever) requiring change in therapy or hospitalisation were classified as treatment failures. Addition of acyclovir and/or fluconazole to antibiotic therapy was regarded as treatment modification rather than treatment failure Adverse events
Notes	Early termination: no Power calculation: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer spreadsheet program"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Hidalgo 1999

Methods	Randomisation: random table Allocation concealment: opaque, sealed envelopes Blinding: no Intention to treat: no

Hidalgo 1999 *(Continued)*

	Exclusions from analysis: 5/100 episodes Follow-up period: end of antibiotic treatment
Participants	Spain 100 episodes of fever and neutropenia in 70 cancer patients Age: range 18-76 yrs Type of malignancy: solid tumour (90%), non-Hodgkin lymphoma (10%)
Interventions	Initial oral Oral: ofloxacin 400mg q12h as outpatients IV: ceftazidime 2g q8h +amikacin 500mg q12h as inpatients
Outcomes	All cause mortality infection-related mortality Treatment failure Treatment failure not due to modification of the primary intervention Lost to follow-up Adverse events (any)
Notes	Journal publication Outcomes in subgroups: FUO, documented infections Definitions of outcomes: Failure: death, persistence or relapse of fever, worsening of infection, shock, continuing positive blood cultures; any modification of antibiotic regimen (addition of antibiotic, antifungal, antiviral agent)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Innes 2003

Methods	Randomisation: no information Allocation concealment: opaque, sealed envelopes Blinding: no information Intention to treat: no Exclusions from analysis: 9/135 episodes Follow-up period: oral treatment: 7-10 days after discharge, IV therapy: end of treatment
Participants	UK, 1997-2000 135 episodes of fever and neutropenia in 111 cancer patients, age range 18-78 yrs Type of malignancy: solid tumour (75%), lymphoma (5%)

Innes 2003 *(Continued)*

Interventions	Initial oral Oral: ciprofloxacin 750mg q12h and amoxicillin 500mg-clavulanate 175mg q8h for 5 days as outpatients IV: gentamicin 80mg q8h and tazocin 4.5mg q8h as inpatients.
Outcomes	All cause mortality infection-related mortality Treatment failure Treatment failure not due to modification of the primary intervention Number of patients who became afebrile Length of hospital stay Lost to follow-up Adverse events (any, requiring discontinuation, causing mortality/morbidity)
Notes	Published and unpublished data. Definitions of outcomes: Failure: death, any modification of antibiotic regimen, recurrence of fever. Reasons for modification:persistant fever, resistant organism or clinical deterioration (for the oral arm also inability to tolerate oral medication) (Cometta 1995, EORTC guidelines)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Kern 1999

Methods	Randomisation: computer program Allocation concealment: central, stratified by centre, type of cancer (haematologic or solid), granulocyte count at entry Blinding: outcomes assessors Intention to treat: yes Exclusions from analysis: 2/370 patients Interim analysis: 2 interim analysis with stopping rules. The study was stopped in the 2nd interim analysis when the boundary for claiming equivalence in the 2 treatment groups had been reached Follow-up period: 30 days following randomisation
Participants	Greece, Spain, Slovak Republic, Turkey, Italy, Luxembourg, Germany, France, Switzerland, Belgium, UK, Czech Republic, Canada, Israel, 1995-1997 370 patients with fever and neutropenia Age: range 5-85 yrs Type of malignancy: solid tumour (68%), lymphoma or chronic leukaemia (32%)
Interventions	Initial oral Oral: ciprofloxacin 750mg q12h (child 15mg/kg if <40kg) +Augmentin 625 q8h (15mg/kg if <40kg) as inpatients

Kern 1999 *(Continued)*

	IV: ceftriaxone 2g (80mg/kg if <25kg) q24h + amikacin 20mg/kg/d as inpatients
Outcomes	All cause mortality Infection-related mortality (death before resolution of fever) Treatment failure Treatment failure not due to modification of the primary intervention Length of febrile episode Duration of therapy Lost to follow-up Adverse events (any)
Notes	Journal publication Outcomes in subgroups: documented infection, severe neutropenia Definitions of outcomes: (Cometta 1996)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Central
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Malik 1992

Methods	Randomisation: no information Allocation concealment: sealed envelopes (opaque not mentioned) Blinding: no information Intention to treat: no Exclusions from analysis: 15/137 patients Follow-up period: 7 days and end of neutropenia
Participants	Pakistan, 1989-1991 137 cancer patients with fever and neutropenia Age: >16 yrs Type of malignancy: leukaemia and lymphoma (55%), solid tumour (20%), aplastic anaemia
Interventions	Initial oral Oral: ofloxacin 400mg/24h IV: amikacin + carbenicillin 400mg/kg/d or cloxacillin 1g q6h or piperacillin 4g q4h Unclear setting

Malik 1992 *(Continued)*

Outcomes	All cause mortality Treatment failure Treatment failure not due to modification of the primary intervention Length of febrile episode (in successfully treated patients) Lost to follow-up Adverse events
Notes	Journal publication Outcomes in subgroups: FUO, documented infections Definitions of outcomes: Failure: death during fever or neutropenia; worsening infection, shock, continuing positive blood culture, persistence of fever unless substantial improvement, any modification of antibiotic regimen (including antiviral or antifungal treatment)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Mullen 1999

Methods	Randomisation: computer program Allocation concealment: no information Blinding: no information Intention to treat: no Exclusions from analysis: 3/76 episodes, of unknown treatment assignment Follow-up period: end of antibiotic treatment
Participants	USA, 1995-1997 76 episodes of fever and neutropenia in 44 cancer patients Age: range 3-20 yrs Type of malignancy: leukaemia (30%), not induction therapy for leukaemia or lymphoma
Interventions	Sequential Oral: single dose of IV ceftazidime 50mg/kg max 2g, change to ciprofluoxacin 12.5mg/kg q12h as outpatients IV: ceftazidime 50mg/kg max 2g q8h as outpatients
Outcomes	All cause mortality Treatment failure Length of febrile episode Length of hospital stay Lost to follow-up Adverse events; ?-are all reported?

Mullen 1999 *(Continued)*

Notes	Journal publication Definitions of outcomes: Failure: hospitalisation for any reason (indications for admission: positive blood culture and >3days fever, >5days fever, emesis, hypersensitivity, life threatening treatment related complications, deterioration)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	

Niho 2004

Methods	Randomisation: random number table Allocation concealment: sealed, opaque envelopes Blinding: no Intention to treat: possible for failure Exclusions from analysis: none
Participants	36 neutropenic patients with 41 febrile episodes, during 1995-2001, in Japan Age: range 51-76 yrs Type of malignancy: all solid tumour
Interventions	Initial oral Oral: ciprofloxacin 200 mg and amoxicillin-clavulanate 375 mg q8h as inpatients IV: ceftazidime 1 g q12h as inpatients
Outcomes	Treatment failure Treatment failure not due to modification Adverse events (discontinuation of therapy) Subgroups: solid tumours, adults, documented infection
Notes	Randomisation of episodes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	

Niho 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were analysed

Paganini 2000

Methods	Randomisation: computer program Allocation concealment: central Blinding: no information Intention to treat: no Exclusions from analysis: 0/154 episodes Follow-up period: 30 days following randomisation
Participants	Argentina, 1997-1998 154 episodes of fever and neutropenia in 124 cancer patients Age: range 9 months -16.6 yrs Type of malignancy: leukaemia (52%), lymphoma (5%), solid tumour (43%)
Interventions	Sequential Oral: IV ceftriaxone 100mg/kg/d q12h +amikacin 15mg/kg/d q24h for 72 hours, change to cefixime 8mg/kg /d as outpatients IV: ceftriaxone 100mg/kg/d q12h +amikacin 15mg/kg/d q24h as outpatients
Outcomes	All cause mortality Treatment failure Treatment failure not due to modification of the primary intervention Length of febrile episode Lost to follow-up Adverse events
Notes	Randomisation of episodes Definitions of outcomes: Failure: re-admission due to recurrence of fever

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Low risk	Central
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

Paganini 2003

Methods	Randomisation: computer program Allocation concealment: central Blinding: no Intention to treat: possible (episodes) Exclusions from analysis: none Follow-up period: episode of fever and neutropenia, at least 7 days
Participants	Argentina, during 2000-2002 177 episodes in 135 children, Type of malignancy: acute leukaemia 59% solid tumours 37.5% lymphoma 4%
Interventions	Sequential Oral: IV ceftriaxone 100 mg/kg + amikacin 15 mg/kg, change to ciprofloxacin 10 mg/kg q12h as outpatients IV: amikacin 15 mg/kg + ceftriaxone 100 mg/kg/d followed by only ceftriaxone 100mg/kg q24h as outpatients
Outcomes	All cause mortality Treatment failure Treatment failure not due to modification of the primary intervention Adverse events (any)
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

Petrilli 2000

Methods	Randomisation generation: no information Allocation concealment: no information Blinding: no information Intention to treat: no Exclusions from analysis: 22/138 episodes Follow-up period: end of antibiotic treatment
Participants	Brazil, 1993-1995 138 episodes of fever and neutropenia in 70 cancer patients

Petrilli 2000 *(Continued)*

	Age: range 3-20 yrs Type of malignancy: solid tumour (91%), lymphoma (4.3%) not receiving high dose chemotherapy
Interventions	Initial oral Oral: ciprofloxacin 12.5 mg/kg/d q12h as outpatients IV: ceftriaxone 100mg/kg/d q24h as outpatients
Outcomes	All cause mortality Treatment failure Treatment failure not due to modification of the primary intervention Length of febrile episode Lost to follow-up Adverse events
Notes	Journal publication Definitions of outcomes: Failure: death, addition of antibiotic, antiviral or antifungal agent. Reasons for addition of antibiotics: persistent fever, clinical deterioration, resistant organism. Addition of antifungal: fever >7 days or suspected fungal 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
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons of attrition and allocation were reported

Rolston 1995

Methods	Randomisation: no information Allocation concealment: no information Blinding: no information Intention to treat: no information Exclusions from analysis: no information Follow-up period: no information
Participants	USA 179 episodes of fever and neutropenia in cancer patients. The numbers of randomised episodes are not specified Age: unspecified Type of malignancy: solid tumour (83%), haematologic malignancy (8%)
Interventions	Initial oral Oral: ciprofloxacin 500mg q8h + amoxicillin-clavulanate 500mg q8h as outpatients

Rolston 1995 *(Continued)*

	IV: aztreonam 2g q8h plus clindamycin 600mg q8h as outpatients
Outcomes	Infectious related mortality Treatment failure
Notes	Conference proceedings Outcomes in subgroups: FUO, documented infections, severe neutropenia, solid tumour, haematologic malignancy

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data on exclusions were reported

Rubenstein 1993

Methods	Randomisation: no information, stratified according to leukaemia Allocation concealment: no information Blinding: outcomes assessors Intention to treat: no Exclusions from analysis: 13/96 episodes Follow-up period: 7 days after end of antibiotic treatment
Participants	USA, 1989-1990 96 episodes of fever and neutropenia in 78 cancer patients Age: 16-74 yrs Type of malignancy: solid tumour (73%) - sarcoma, breast cancer, melanoma, hematologic malignancy (26%) - acute and chronic leukemia, lymphoma, myeloma, other
Interventions	Initial oral Oral: ciprofloxacin 750mg q8h + clindamycin 600mg q8h as outpatients IV: aztreonam 2gr q8h +clindamycin 600mg q8h as outpatients
Outcomes	Infection-related mortality Treatment failure Lost to follow-up Adverse events (requiring discontinuation, causing mortality/morbidity)
Notes	Journal publication Outcomes in subgroups: FUO, documented infections, solid tumours, haematologic malignancy Definitions of outcomes: Failure: patients with positive cultures who remained febrile after 3 days, or with negative culture febrile after 5 days

Risk of bias

Bias	Authors' judgement	Support for judgement

Rubenstein 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Samonis 1997

Methods	Randomisation: no information Allocation concealment: no information Blinding: no Intention to treat: no Exclusions from analysis: 12/195 patients Follow-up period: end of antibiotic treatment, median 6 days (5-15)
Participants	Greece, 1994-1996 195 cancer patients with fever and neutropenia Age: range 28-75 yrs Type of malignancy: solid tumour (95%), lymphoma (5%)
Interventions	Initial oral Oral: ampicillin-sulbactam +375mg x4 plus ciprofloxacin 250 mg x4 as outpatients IV: ceftazidime 1g x3 plus amikacin 500mg x2 as inpatients
Outcomes	All cause mortality Treatment failure Treatment failure not due to modification of the primary intervention Length of febrile episode Duration of therapy Lost to follow-up Adverse events
Notes	Conference proceedings The full article was sent by the authors Outcomes in sub-groups: FUO Definitions of outcomes: Failure: death or modification of antibiotic regimen

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias)	Low risk	Allocation of patients excluded after randomisation was reported

Samonis 1997 *(Continued)*
All outcomes

Sebban 2009*

Methods	Randomisation: no information Allocation concealment: adequate Blinding: no Intention to treat: no Exclusions from analysis: 2/96 episodes
Participants	96 episodes in 90 patients, during 2003-2005, multi-centre Age: mean 52 years, median 54 years Type of malignancy: 30% lymphoma; 35% solid tumour no metastasis; 34% solid tumour with metastasis
Interventions	Oral: moxifloxacin 400 mg once daily ceftriaxone 2 gr intravenously as a single daily dose
Outcomes	Global success of the at-home antibiotic therapy Effectiveness of the antibiotic monotherapy Quality of life Toxicity
Notes	Early termination due to recruitment problems Power calculation reported, a non-inferiority study Definitions of outcomes: Global success of the at-home antibiotic therapy. The overall strategy (antibiotics and early hospital discharge) was considered a success not only when the effectiveness of the antibiotic therapy was achieved (as defined by the resolution of fever and of the possible clinical or microbiological manifestations of the infection) but also in the presence of the following criteria: early hospital discharge (within 24 or 48 h), no death from any cause, no sign or symptom of clinical deterioration requiring hospital readmission, no initial infection by a pathogen resistant in vitro to the antibiotics tested, no modification of initial anti-biotherapy, no relapse or new infection during antibiotic treatment, no toxic reaction to the antibiotic requiring discontinuation of treatment, and no re-hospitalisation of the patient for any cause. Effectiveness of the antibiotic monotherapy (as evidenced by the lack of need for any additional antibiotics besides ceftriaxone or moxifloxacin)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"Randomization was centralized and was stratified according to the participating center"

Sebban 2009* *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and allocation were reported

Shenep 2001

Methods	Randomisation: computer program, stratified by hierarchical rules according to absolute neutrophil count<100 cells/m3, expected duration of neutropenia ≥5days, non-standard initial empiric antibiotic regimen, presence of indwelling venous catheter, diagnosis of acute myeloid leukaemia, persistent fever at randomisation Allocation concealment: central pharmacy Blinding: treatment providers Intention to treat: yes Exclusions from analysis: 0/200 episodes Follow-up period: end of antibiotic treatment, 4 interim analysis
Participants	USA, 1991-1995 200 episodes of fever and neutropenia in 156 cancer patients Age: range 1.3-19 yrs Type of malignancy: solid tumour (38%), acute leukaemia (54%), other
Interventions	Sequential Oral: IV tobramycin (or amikacin) + ticarcillin +vancomycin OR ceftazidime +vancomycin until randomisation, change to cefixime 4mg/kg q12h as inpatients IV: tobramycin q6h 60mg/m2 (or amikacin) + ticarcillin 2.25g/m2 max 18g/d + vancomycin 300mg/m2 max 4g/d or ceftazidime 1.5g/m2 +vancomycin if renal failure or nephrotoxic chemotherapy as inpatients All received prophylactic TMP-SMZ
Outcomes	All cause mortality Treatment failure Treatment failure not due to modification of the primary intervention Lost to follow-up Adverse events (any, requiring discontinuation)
Notes	Journal publication Outcomes in subgroups: severe neutropenia Definitions of outcomes: Failure: death, addition of antibiotics, recurrence of fever, bacteraemia, documented or suspected localized bacterial infection, a new pulmonary infiltrate other than atelectasis, colonization with MRSA or P.auroginosa detected after randomisation, sepsis, severe mucositis in association with fever ≥38.3 or discontinuing participation by patient or their physician

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

Shenep 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included in analysis

Velasco 1995

Methods	Randomisation: random number table Allocation concealment: sealed opaque envelopes Blinding: no Intention to treat: no Exclusions from analysis: 4/108 episodes Follow-up period: end of antibiotic treatment
Participants	Brasil, 1991-1992 108 episodes of fever and neutropenia in 76 cancer patients Age: ≥16 yrs Type of malignancy: solid tumour (79%), non-lymphoblastic lymphoma (21%)
Interventions	Initial oral Oral: ciprofloxacin 500mg q8h +penicillin V 1 million u q6h as inpatients IV: amikacin 5mg/kg q8h +carbenicillin 500mg/kg/6 q4h or ceftazidime 100mg/kg q8h as inpatients
Outcomes	All cause mortality Infection-related mortality Treatment failure Treatment failure not due to modification of the primary intervention Length of hospital stay Lost to follow-up Adverse events (any, requiring discontinuation)
Notes	Journal publication Outcomes in subgroups: severe neutropenia, solid tumour, lymphoma Definitions of outcomes: Failure: death from infection or antibiotic modification due to infection progression within first 72 hours, breakthrough bacteraemia, fever persistence without clinical improvement or severe drug reaction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	

Velasco 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Allocation of excluded patients was reported

General exclusion criteria:
haemodynamic instability, hypotension; altered mental status; respiratory failure; poor clinical condition, renal failure, abnormal liver function tests, no ability to swallow or take oral medication (vomiting, severe mucositis); hypersensitivity; pregnancy, lactation
yrs = years
vs = versus
FUO = fever of unknown origin

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmed 2007	IV antibiotics in both groups
Ammann 2004	Not a randomised controlled trial, correspondence to Paganini 2003
Aquino 1997	A retrospective trial
Aquino 2000	Prospective, not randomised clinical trial Oral ciprofloxacin for the outpatient treatment of patients with fever and neutropenia
Bash 1994	Prospective, not randomised clinical trial Antibiotics discontinuation before neutrophil count recovery
Berrahal 1996	Prospective, not randomised clinical trial Evaluating the feasibility and the efficacy of combined IV ticarcillin-clavulanic acid and IV ciprofloxacin with a switch to oral ciprofloxacin at the 48th hour
Chamilos 2005	Prospective, not randomised clinical trial
Chernobelski	Prospective, not randomised clinical trial
Cometta 2004	A review
Copper 2011	A review, not a randomised controlled trial
Cornelissen 1995	Prospective, not randomised clinical trial Sequential IV antibiotics to oral antibiotics for the treatment of fever and neutropenia
Dommett 2009	Prospective clinical trial, not randomised; step-down to oral antibiotics
Escalante 2004	Prospective clinical trial, not randomised
Flores 2010	Intervention: pegfilgrastim, not antibiotics
Freifeld 1997	A review
Freifeld 2008	Not a randomised controlled trial
Freifeld 2011	Editorial, not a randomised controlled trial
Gardembas-Pain 1991	Prospective, not randomised clinical trial

Study	Reason for exclusion
	Oral treatment for treatment of patients with fever and neutropenia
Guyotat 1985	No fever for inclusion in trial Intervention: oral antibiotics (gentamycin , colistine and nystatin) was compared to oral antibiotics regimen including vancomycin Randomised controlled trial
Hendricks 2011	Home intravenous antibiotic treatment compared to continued inpatient care
Horowitz 1996	Prospective, not randomised clinical trial IV antibiotics for 5 days and then change to oral ciprofloxacin treatment of patients with fever and neutropenia
IATCG-EORTC 1994	No fever for inclusion in trial Randomised controlled trial Intervention: prophylactic penicillin V plus perfloxacin versus placebo plus perfloxacin for neutropenic non-febrile patients
Kamana 2005	An observational study
Kern 2006	A review
Kibbler 1987	Prospective, not randomised clinical trial IV antibiotics were given to both treatment arms. Addition of IV ciprofloxacin for the treatment of fever and neutropenia
Klaassen 2000	Intervention: oral antibiotic was compared to placebo (no treatment) Randomised placebo-controlled trial Population: 'low risk' paediatric oncology patients with fever and neutropenia
Klastersky 2006	An observational, non-randomised study
Lau 1994	Prospective, not randomised clinical trial Sequential IV-oral antibiotics for the treatment of patients with fever and neutropenia
Leverger 2004	A review
Luthi 2012	An observational study of children with febrile neutropenia, non-randomised study
Malik 1994	Prospective, not randomised clinical trial Oral ofloxacin for the treatment of patients with fever and neutropenia
Malik 1995	Intervention: oral ofloxacin as inpatients versus oral ofloxacin as outpatients Randomised controlled trial
Malik 1997	Prospective, not randomised clinical trial Oral ofloxacin for the treatment of patients with fever and neutropenia
Marra 2000	Prospective, not randomised clinical trial Step-down in the dosage of parenteral ciprofloxacin and change to oral ciprofloxacin when criteria were met
Meunier 1991	No oral treatment arm Randomised controlled trial IV ciprofloxacin versus IV piperacillin+amikacin for the treatment of patients with fever and neutropenia

Study	Reason for exclusion
Minotti 1999	Included cancer patients with fever non-neutropenic and neutropenic
Montalar Salcedo1999	Prospective, not randomised clinical trial Ofloxacin first intravenously and change to orally for the treatment of patients with fever and neutropenia
Mullen 2001	A review
Mustafa 1996	Prospective, not randomised clinical trial IV ceftriaxone in outpatient setting for the treatment of patients with fever and neutropenia
Nepokul'chitskaia	Prospective, not randomised clinical trial Oral antibiotics for the treatment of patients with fever and neutropenia
Paganini 2001a	Intervention: sequential IV to oral antibiotics was given for both trial arms Randomised controlled trial
Paganini 2001b	Prospective, not randomised clinical trial Sequential IV-oral antibiotic therapy for the treatment of patients with fever and neutropenia
Papadimitris 1999	Prospective, not randomised clinical trial Oral antibiotics for the treatment of patients with fever and neutropenia
Petrilli 2007	Prospective, non-randomised clinical trial
Quezada 2007	Not a randomised controlled trial
Rapoport 1999	All patients received IV antibiotics Randomised controlled trial Early hospital discharge versus in-patient care of patients with fever and neutropenia
Rolston 2006	Prospective, non-randomised clinical trial
Rolston 2010	A prospective study with no control group, not a randomised controlled trial
Santolaya 1997	Intervention: oral antibiotics was compared to no treatment (discontinuation of IV antibiotics before recovery of neutrophil count, no oral antibiotics were given after stopping IV therapy) Randomised controlled trial
Santolaya 2004	Outpatient versus inpatient treatment. All patients received IV ceftriaxone
Sato 2008	No oral antibiotic treatment group
Slavin 2007	All patients received IV antibiotics RCT
Talcott 2011	Same antibiotic in the 2 groups
Tamura 2005	A review
Timmers 2007	Prophylactic antibiotics (no patients with fever)
Uzun 1999	A review; not RCT
Vallejo 1997	Prospective, not randomised clinical trial

Study	Reason for exclusion
	Sequential intravenous-oral ciprofluoxacin plus amoxicillin/clavulanate for febrile non severe neutropenic patients
Wacker 1997	Prospective, not randomised clinical trial Early discharge and discontinuing antibiotics in the treatment of patients with fever and neutropenia

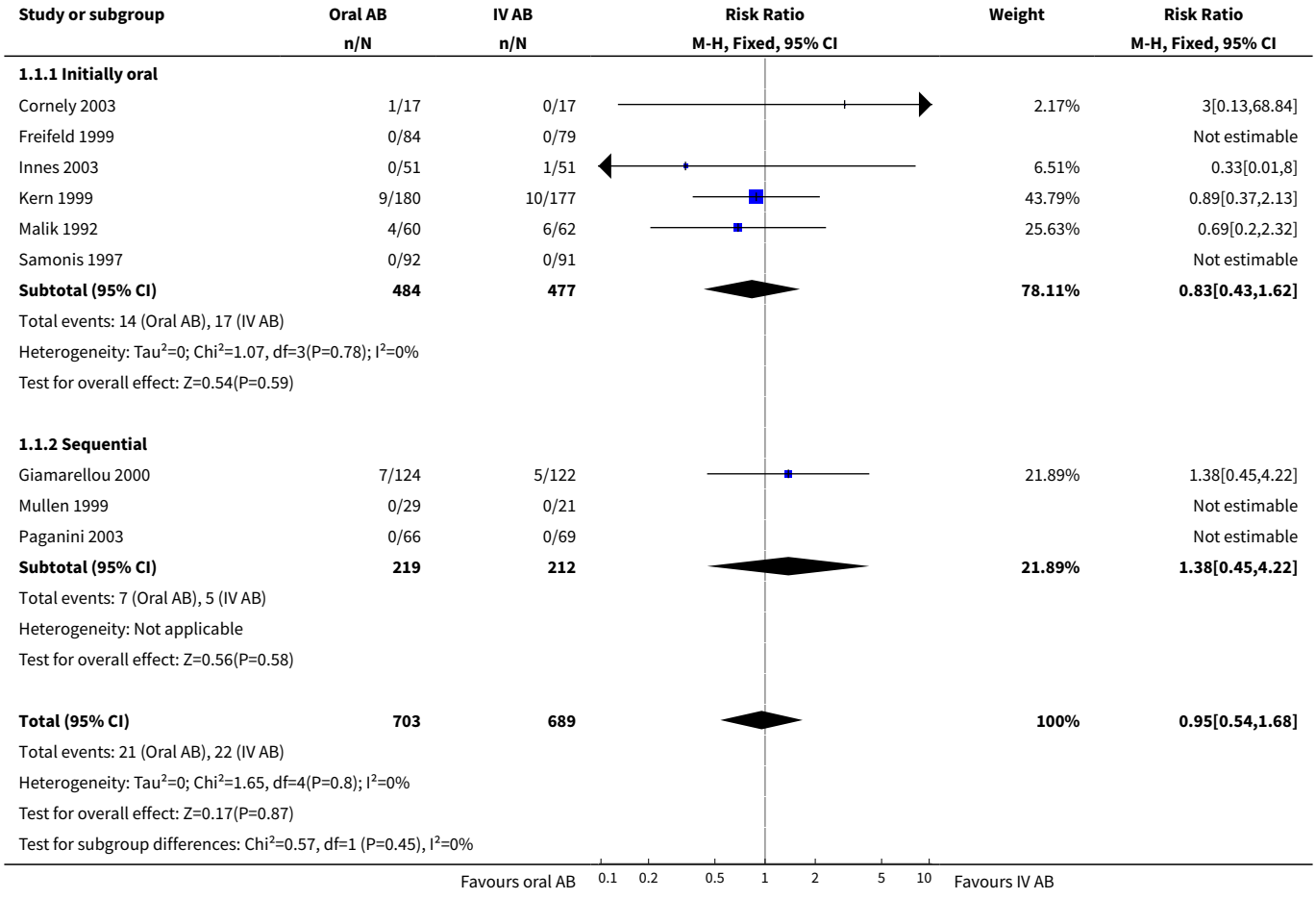
DATA AND ANALYSES

Comparison 1. Oral versus intravenous antibiotic therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	9	1392	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.54, 1.68]
1.1 Initially oral	6	961	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.43, 1.62]
1.2 Sequential	3	431	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.45, 4.22]
2 Treatment failure	22	3142	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.06]
2.1 Initially oral treatment	16	2196	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.03]
2.2 Sequential IV to oral treatment	6	946	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.90, 1.27]
3 Treatment failure - per protocol analysis	22	2912	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.86, 1.11]
3.1 Initially oral treatment	16	1991	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.10]
3.2 Sequential IV to oral treatment	6	921	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.29]
4 Adverse events requiring discontinuation of antibiotics	15	1823	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.61, 3.46]
4.1 Initially oral treatment	10	1064	Risk Ratio (M-H, Random, 95% CI)	2.78 [1.14, 6.75]
4.2 Sequential IV to oral treatment	5	759	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.25]
5 Gastrointestinal adverse events ('post-protocol' analysis)	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Initially oral treatment	11	1400	Risk Ratio (M-H, Fixed, 95% CI)	4.49 [2.87, 7.04]
5.2 Sequential IV to oral treatment	4	784	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [1.03, 7.66]

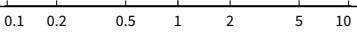
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Lost to follow-up	19	2810	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.10]
7 Treatment failure not dt modification in update	21	3041	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.06]
7.1 Initially oral treatment	15	2095	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.04]
7.2 Sequential IV to oral treatment	6	946	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.25]

Analysis 1.1. Comparison 1 Oral versus intravenous antibiotic therapy, Outcome 1 Mortality.



Analysis 1.2. Comparison 1 Oral versus intravenous antibiotic therapy, Outcome 2 Treatment failure.

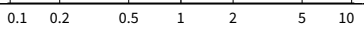
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Initially oral treatment					
Brack 2012*	7/33	9/36		1.93%	0.85[0.36,2.02]
Cagol 2009*	22/43	22/48		4.66%	1.12[0.73,1.71]
Cornely 2003	4/17	2/17		0.45%	2[0.42,9.5]
Freifeld 1999	60/142	73/142		16.38%	0.82[0.64,1.06]
Gupta 2009*	7/62	7/61		1.58%	0.98[0.37,2.64]
Hidalgo 1999	12/50	9/50		2.02%	1.33[0.62,2.88]
Innes 2003	12/68	14/67		3.16%	0.84[0.42,1.69]
Kern 1999	45/186	49/184		11.05%	0.91[0.64,1.29]
Malik 1992	36/68	36/69		8.02%	1.01[0.74,1.39]
Niho 2004	2/22	4/19		0.96%	0.43[0.09,2.1]
Petrilli 2000	19/68	27/70		5.97%	0.72[0.45,1.17]
Rolston 1995	9/89	12/90		2.68%	0.76[0.34,1.71]
Rubenstein 1993	14/49	6/47		1.37%	2.24[0.94,5.33]
Samonis 1997	12/97	15/98		3.35%	0.81[0.4,1.64]
Sebban 2009*	11/49	13/47		2.98%	0.81[0.4,1.63]
Velasco 1995	3/55	8/53		1.83%	0.36[0.1,1.29]
Subtotal (95% CI)	**1098**	**1098**		**68.4%**	**0.91[0.79,1.03]**
Total events: 275 (Oral antibiotics), 306 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=12.26, df=15(P=0.66); I^2=0%					
Test for overall effect: Z=1.46(P=0.14)					
1.2.2 Sequential IV to oral treatment					
Flaherty 1989	29/49	15/30		4.17%	1.18[0.77,1.81]
Giamarellou 2000	69/131	72/132		16.09%	0.97[0.77,1.21]
Mullen 1999	12/40	7/33		1.72%	1.41[0.63,3.18]
Paganini 2000	1/74	2/80		0.43%	0.54[0.05,5.84]
Paganini 2003	19/88	14/89		3.12%	1.37[0.74,2.56]
Shenep 2001	28/100	27/100		6.06%	1.04[0.66,1.63]
Subtotal (95% CI)	**482**	**464**		**31.6%**	**1.07[0.9,1.27]**
Total events: 158 (Oral antibiotics), 137 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=2.4, df=5(P=0.79); I^2=0%					
Test for overall effect: Z=0.73(P=0.47)					
Total (95% CI)	**1580**	**1562**		**100%**	**0.96[0.86,1.06]**
Total events: 433 (Oral antibiotics), 443 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=16.32, df=21(P=0.75); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
Test for subgroup differences: Chi^2=2.14, df=1 (P=0.14), I^2=53.24%					



Analysis 1.3. Comparison 1 Oral versus intravenous antibiotic therapy, Outcome 3 Treatment failure - per protocol analysis.

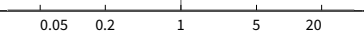
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Initially oral treatment					
Brack 2012*	4/27	8/34		2.16%	0.63[0.21,1.87]

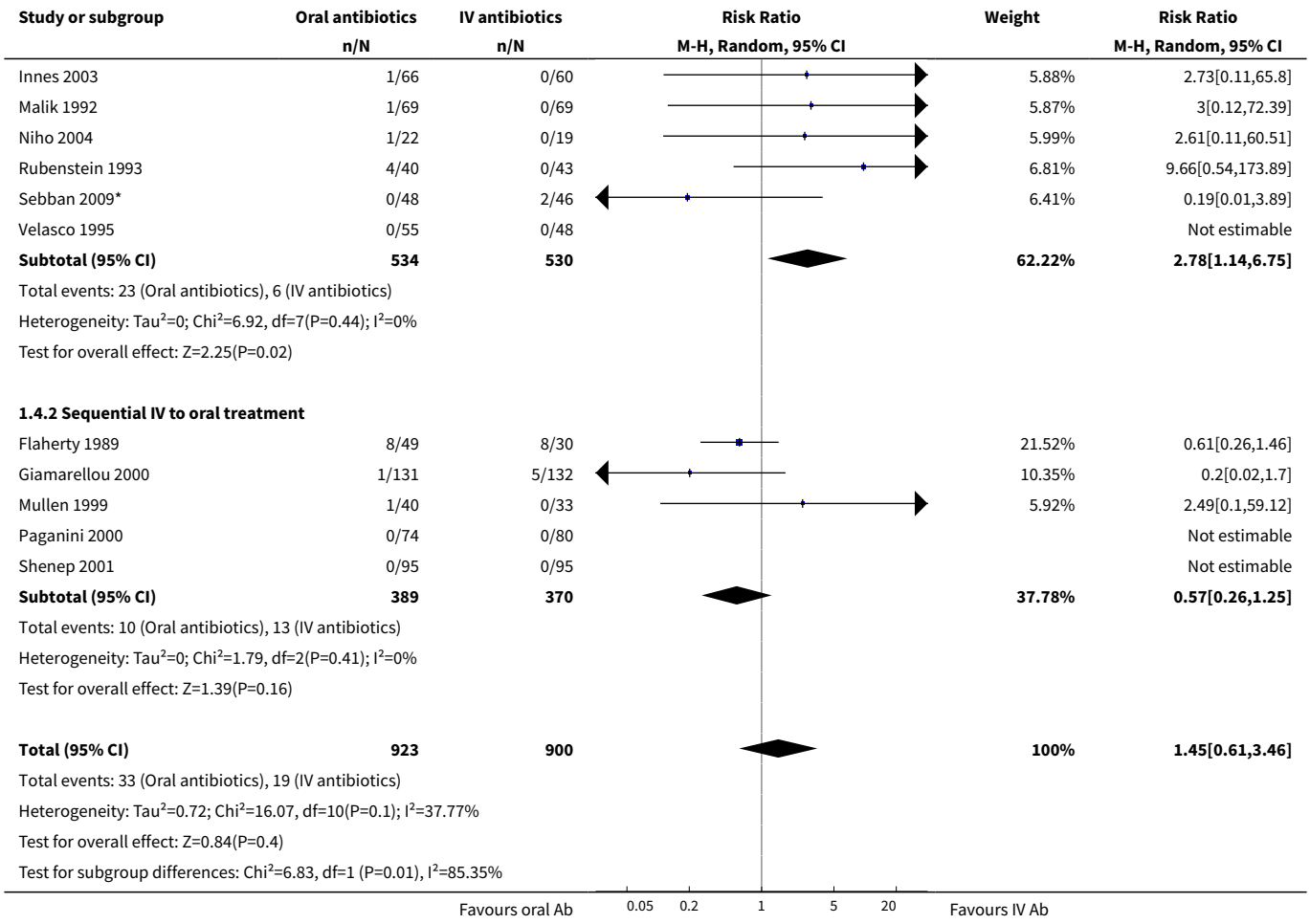
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cagol 2009*	22/43	22/48		6.35%	1.12[0.73,1.71]
Cornely 2003	4/17	2/17		0.61%	2[0.42,9.5]
Freifeld 1999	34/116	47/116		14.35%	0.72[0.51,1.04]
Gupta 2009*	6/61	4/58		1.25%	1.43[0.42,4.8]
Hidalgo 1999	10/48	6/47		1.85%	1.63[0.64,4.13]
Innes 2003	10/66	6/60		1.92%	1.52[0.59,3.92]
Kern 1999	23/161	23/151		7.25%	0.94[0.55,1.6]
Malik 1992	28/60	29/62		8.71%	1[0.68,1.46]
Niho 2004	2/22	4/19		1.31%	0.43[0.09,2.1]
Petrilli 2000	10/59	14/57		4.35%	0.69[0.33,1.43]
Rolston 1995	9/89	12/90		3.64%	0.76[0.34,1.71]
Rubenstein 1993	5/40	2/43		0.59%	2.69[0.55,13.08]
Samonis 1997	7/92	8/91		2.46%	0.87[0.33,2.29]
Sebban 2009*	10/48	12/46		3.74%	0.8[0.38,1.67]
Velasco 1995	3/55	3/48		0.98%	0.87[0.18,4.12]
Subtotal (95% CI)	**1004**	**987**		**61.5%**	**0.93[0.78,1.1]**
Total events: 187 (Oral antibiotics), 202 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=10.77, df=15(P=0.77); I^2=0%					
Test for overall effect: Z=0.85(P=0.39)					
1.3.2 Sequential IV to oral treatment					
Flaherty 1989	29/49	15/30		5.68%	1.18[0.77,1.81]
Giamarellou 2000	62/124	62/124		18.93%	1[0.78,1.28]
Mullen 1999	8/40	7/33		2.34%	0.94[0.38,2.33]
Paganini 2000	1/74	2/80		0.59%	0.54[0.05,5.84]
Paganini 2003	19/88	14/89		4.25%	1.37[0.74,2.56]
Shenep 2001	23/95	22/95		6.72%	1.05[0.63,1.74]
Subtotal (95% CI)	**470**	**451**		**38.5%**	**1.07[0.88,1.29]**
Total events: 142 (Oral antibiotics), 122 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=1.5, df=5(P=0.91); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**1474**	**1438**		**100%**	**0.98[0.86,1.11]**
Total events: 329 (Oral antibiotics), 324 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=13.38, df=21(P=0.89); I^2=0%					
Test for overall effect: Z=0.29(P=0.77)					
Test for subgroup differences: Chi^2=1.13, df=1 (P=0.29), I^2=11.29%					



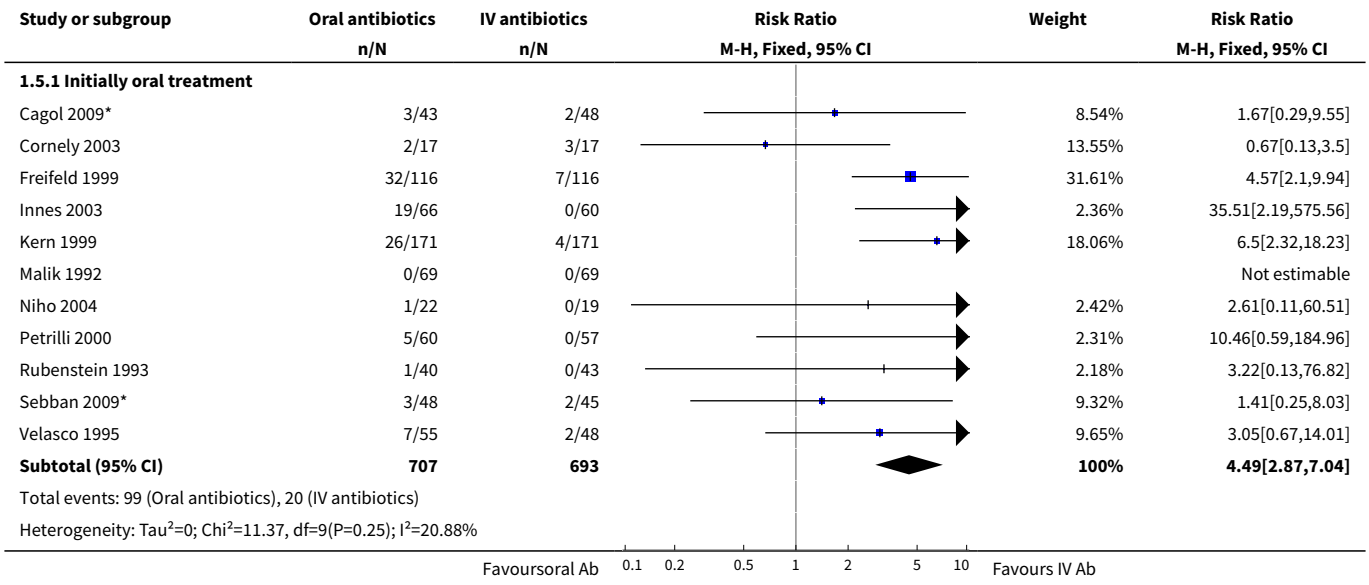
Analysis 1.4. Comparison 1 Oral versus intravenous antibiotic therapy, Outcome 4 Adverse events requiring discontinuation of antibiotics.

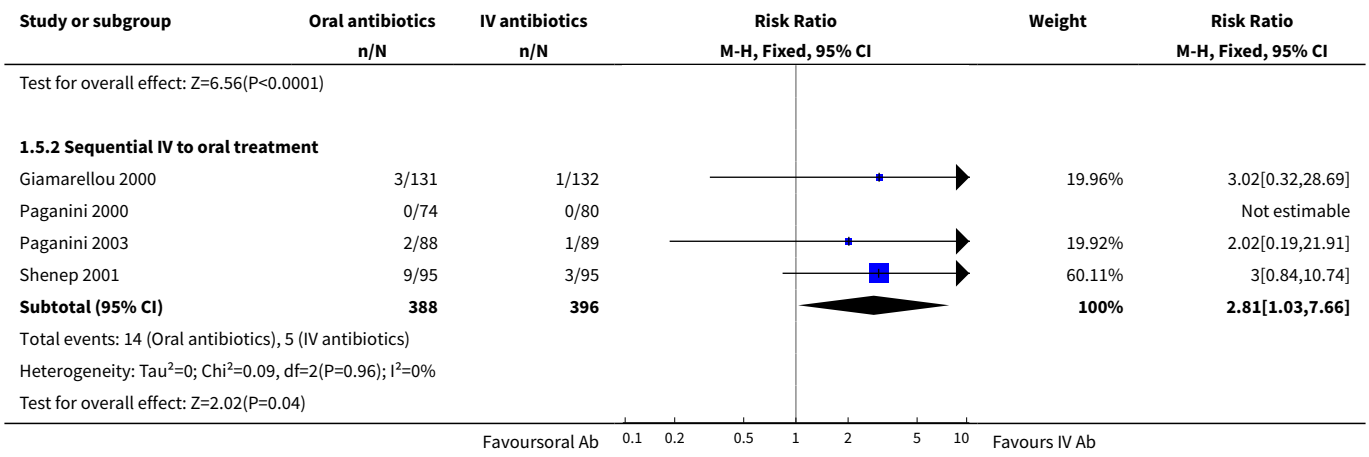
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Initially oral treatment					
Brack 2012*	0/27	1/34		5.94%	0.42[0.02,9.84]
Cagol 2009*	5/43	2/48		14.33%	2.79[0.57,13.65]
Freifeld 1999	11/116	1/116		10.99%	11[1.44,83.83]
Hidalgo 1999	0/48	0/47			Not estimable



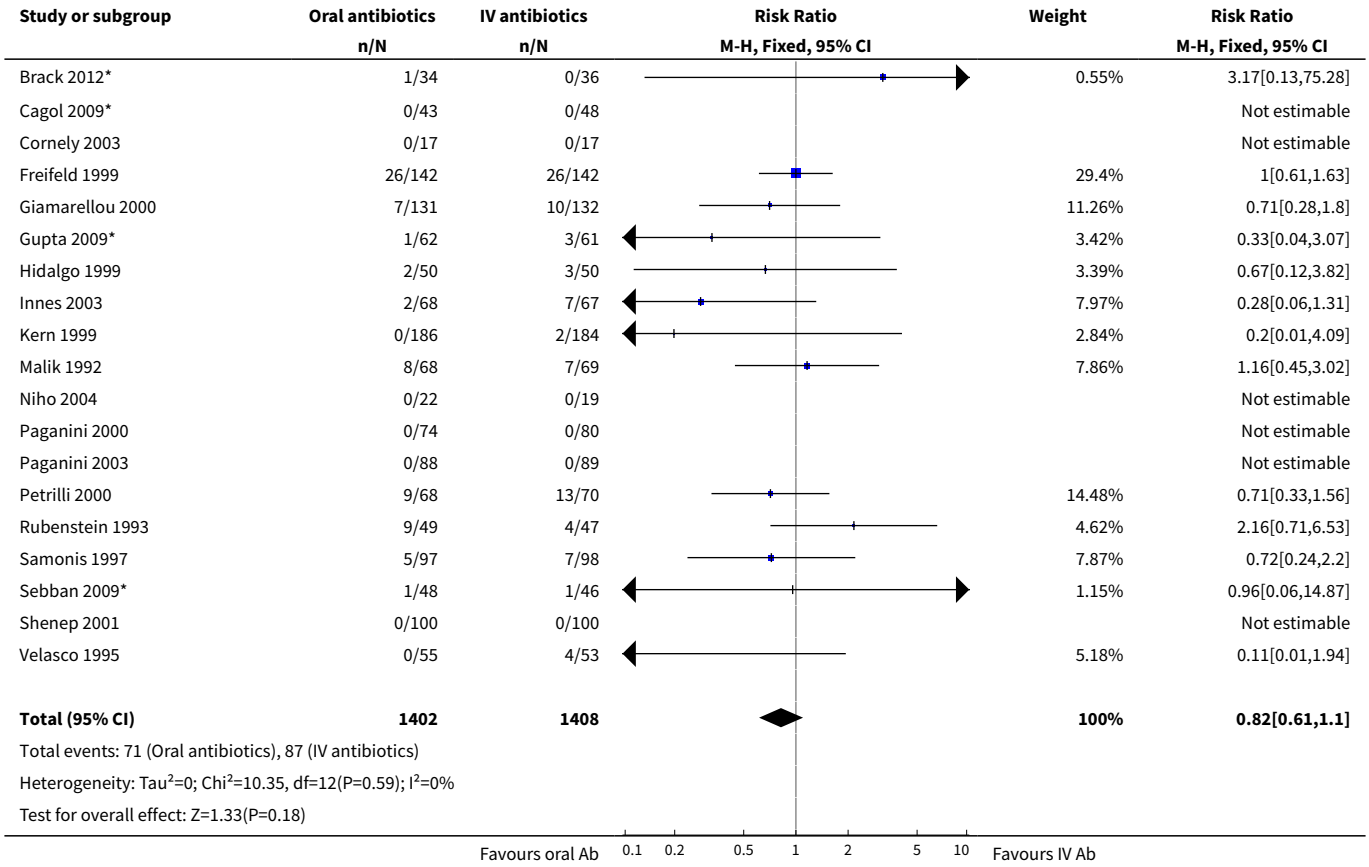


Analysis 1.5. Comparison 1 Oral versus intravenous antibiotic therapy, Outcome 5 Gastrointestinal adverse events ('post-protocol' analysis).

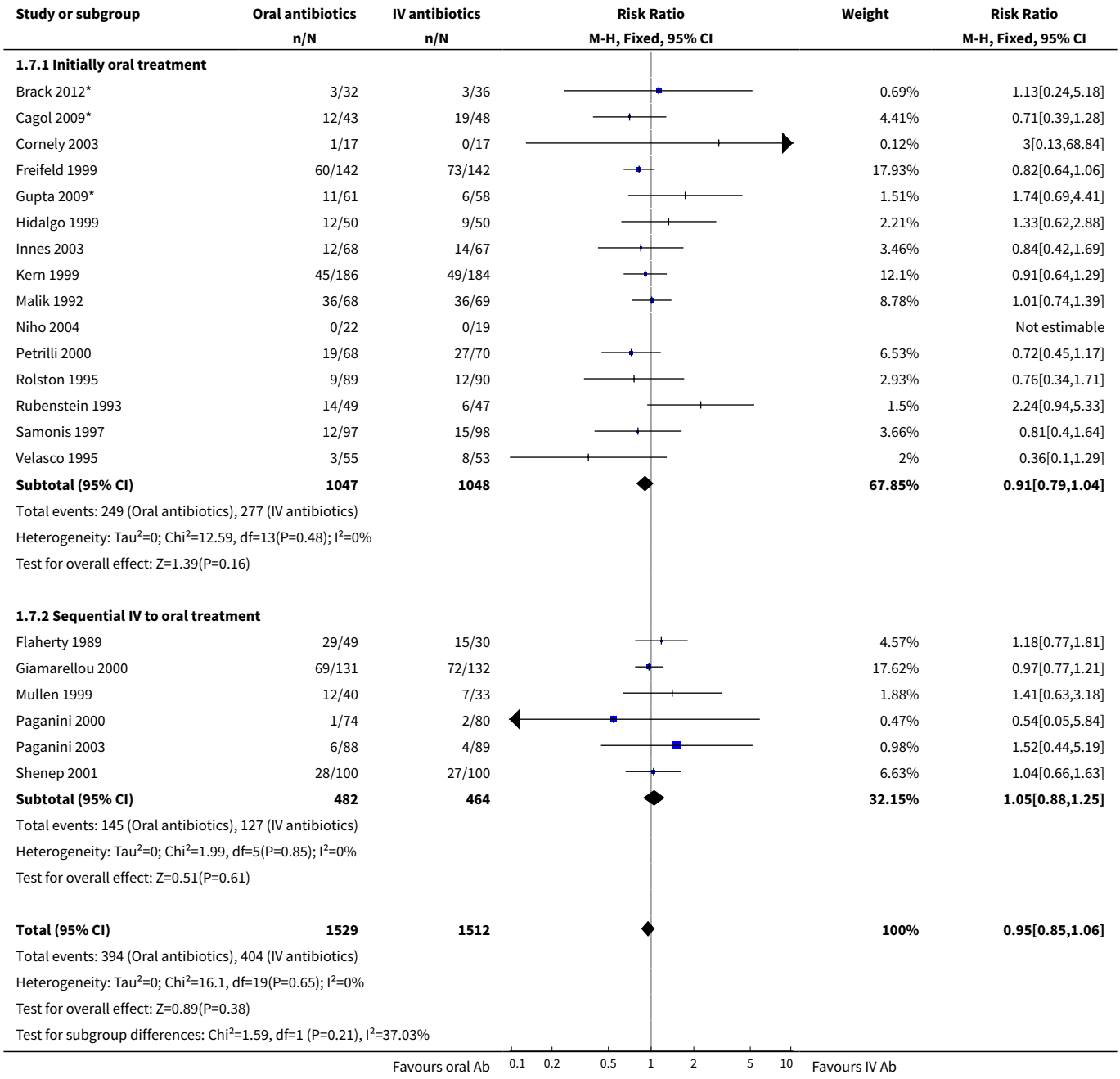




Analysis 1.6. Comparison 1 Oral versus intravenous antibiotic therapy, Outcome 6 Lost to follow-up.



Analysis 1.7. Comparison 1 Oral versus intravenous antibiotic therapy, Outcome 7 Treatment failure not dt modification in update.



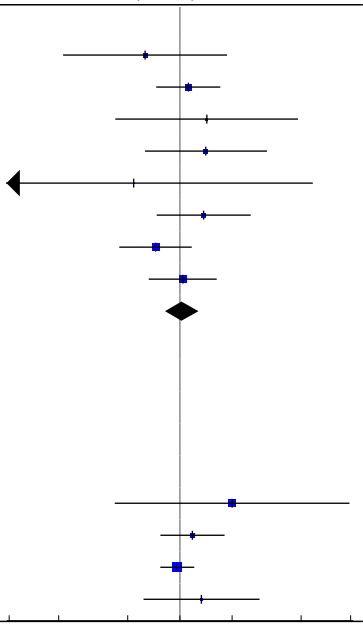
Comparison 2. Oral versus intravenous antibiotic therapy - subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure - age	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Children	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Adults	12	1652	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.12]
2 Treatment failure - source of infection	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Unexplained fever	10	924	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.33]
2.2 Documented infection	10	641	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.19]
3 Treatment failure - severity of neutropenia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Absolute neutrophil count >=10^9/L	3	328	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.45, 0.98]
3.2 Absolute neutrophil count <10^9/L	3	370	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.76, 1.49]
4 Treatment failure - type of malignancy	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Solid tumour	7	990	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.12]
4.2 Haemetologic malignancy	4	412	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.28]

Analysis 2.1. Comparison 2 Oral versus intravenous antibiotic therapy - subgroup analysis, Outcome 1 Treatment failure - age.

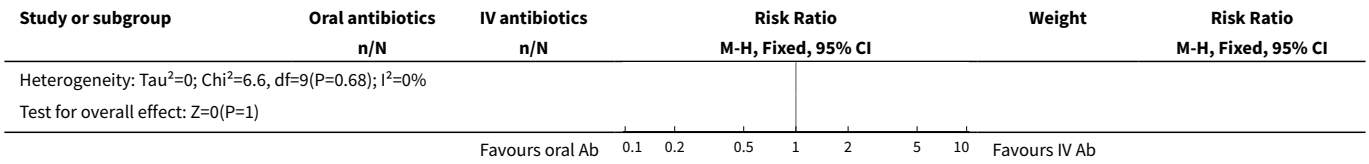
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Children					
Brack 2012*	4/27	8/34		6.49%	0.63[0.21,1.87]
Cagol 2009*	22/43	22/48		19.06%	1.12[0.73,1.71]
Gupta 2009*	6/61	4/58		3.76%	1.43[0.42,4.8]
Mullen 1999	12/40	7/33		7.03%	1.41[0.63,3.18]
Paganini 2000	1/74	2/80		1.76%	0.54[0.05,5.84]
Paganini 2003	19/88	14/89		12.76%	1.37[0.74,2.56]
Petrilli 2000	19/68	27/70		24.39%	0.72[0.45,1.17]
Shenep 2001	28/100	27/100		24.75%	1.04[0.66,1.63]
Subtotal (95% CI)	**501**	**512**		**100%**	**1.02[0.82,1.28]**
Total events: 111 (Oral antibiotics), 111 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=4.92, df=7(P=0.67); I^2=0%					
Test for overall effect: Z=0.21(P=0.83)					
2.1.2 Adults					
Cornely 2003	4/17	2/17		0.81%	2[0.42,9.5]
Flaherty 1989	29/49	15/30		7.56%	1.18[0.77,1.81]
Giamarellou 2000	69/131	72/132		29.14%	0.97[0.77,1.21]
Hidalgo 1999	12/50	9/50		3.66%	1.33[0.62,2.88]



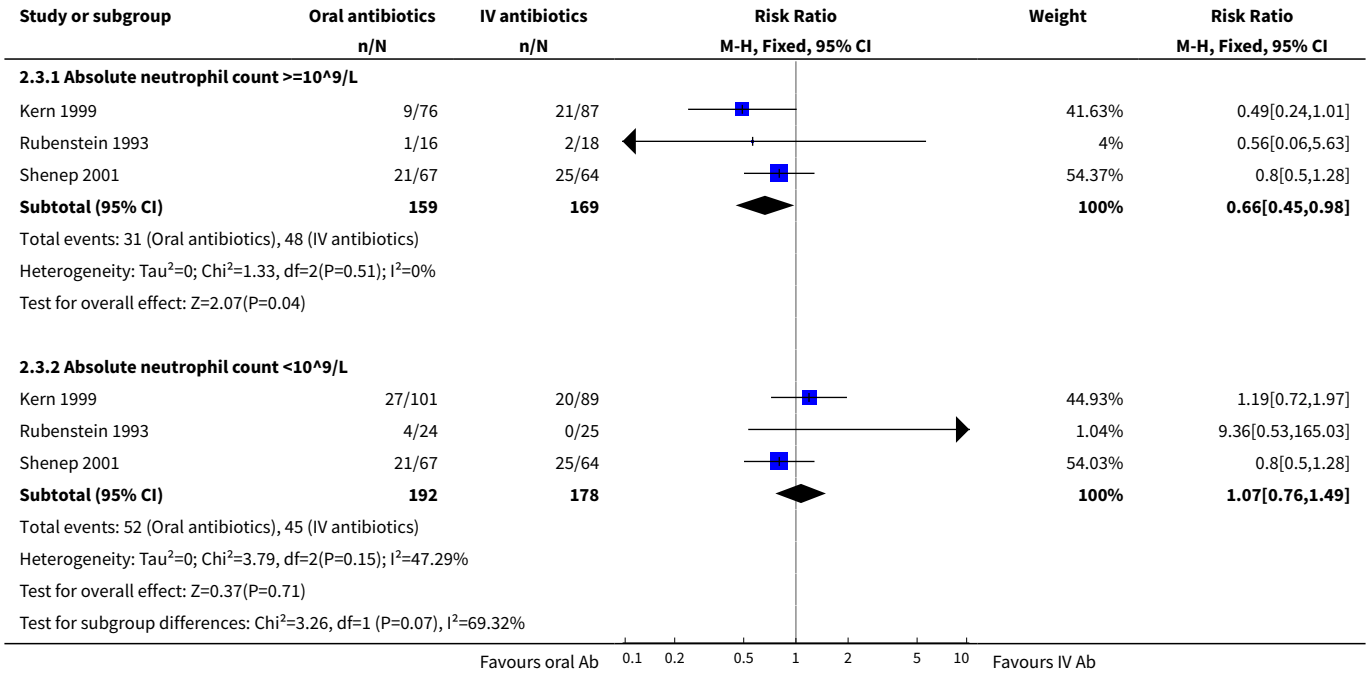
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Innes 2003	12/68	14/67		5.73%	0.84[0.42,1.69]
Kern 1999	45/186	49/184		20.01%	0.91[0.64,1.29]
Malik 1992	36/68	36/69		14.52%	1.01[0.74,1.39]
Niho 2004	2/22	4/19		1.74%	0.43[0.09,2.1]
Rubenstein 1993	14/49	6/47		2.49%	2.24[0.94,5.33]
Samonis 1997	12/97	15/98		6.06%	0.81[0.4,1.64]
Sebban 2009*	10/48	12/46		4.98%	0.8[0.38,1.67]
Velasco 1995	3/55	8/53		3.31%	0.36[0.1,1.29]
Subtotal (95% CI)	**840**	**812**		**100%**	**0.98[0.85,1.12]**
Total events: 248 (Oral antibiotics), 242 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=10.05, df=11(P=0.53); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.72), I^2=0%					

Analysis 2.2. Comparison 2 Oral versus intravenous antibiotic therapy - subgroup analysis, Outcome 2 Treatment failure - source of infection.

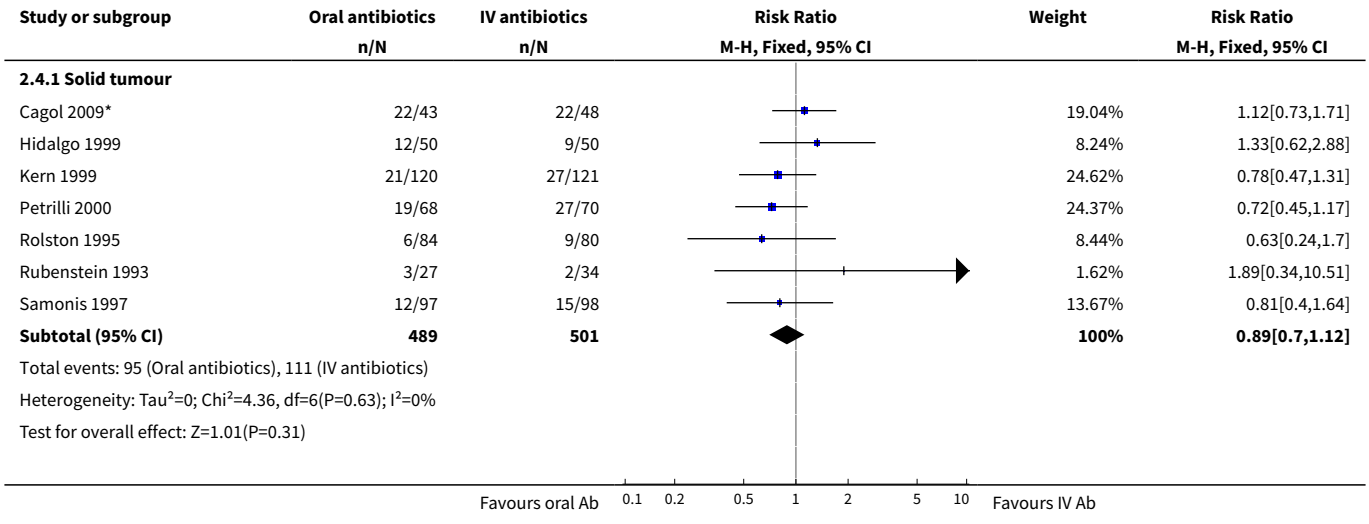
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Unexplained fever					
Cornely 2003	2/13	2/13		2.56%	1[0.16,6.07]
Freifeld 1999	12/79	7/70		9.51%	1.52[0.63,3.64]
Giamarellou 2000	32/56	32/57		40.62%	1.02[0.74,1.41]
Hidalgo 1999	2/31	4/34		4.89%	0.55[0.11,2.79]
Kern 1999	15/108	18/116		22.23%	0.9[0.48,1.69]
Malik 1992	6/24	8/26		9.84%	0.81[0.33,2]
Niho 2004	0/18	0/10			Not estimable
Rolston 1995	5/30	3/28		3.97%	1.56[0.41,5.91]
Rubenstein 1993	2/24	1/27		1.21%	2.25[0.22,23.28]
Samonis 1997	4/81	4/79		5.19%	0.98[0.25,3.77]
Subtotal (95% CI)	**464**	**460**		**100%**	**1.03[0.79,1.33]**
Total events: 80 (Oral antibiotics), 79 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=2.6, df=8(P=0.96); I^2=0%					
Test for overall effect: Z=0.21(P=0.83)					
2.2.2 Documented infection					
Cornely 2003	2/4	0/4		0.4%	5[0.31,79.94]
Freifeld 1999	22/37	31/46		22.31%	0.88[0.63,1.23]
Giamarellou 2000	38/68	37/65		30.55%	0.98[0.73,1.32]
Hidalgo 1999	6/14	4/16		3.01%	1.71[0.6,4.86]
Kern 1999	21/69	23/60		19.86%	0.79[0.49,1.28]
Malik 1992	22/36	21/36		16.95%	1.05[0.72,1.53]
Niho 2004	2/6	4/9		2.58%	0.75[0.2,2.88]
Rolston 1995	3/61	0/55		0.42%	6.32[0.33,119.73]
Rubenstein 1993	3/16	1/16		0.81%	3[0.35,25.87]
Samonis 1997	3/11	4/12		3.09%	0.82[0.23,2.87]
Subtotal (95% CI)	**322**	**319**		**100%**	**1[0.84,1.19]**
Total events: 122 (Oral antibiotics), 125 (IV antibiotics)					

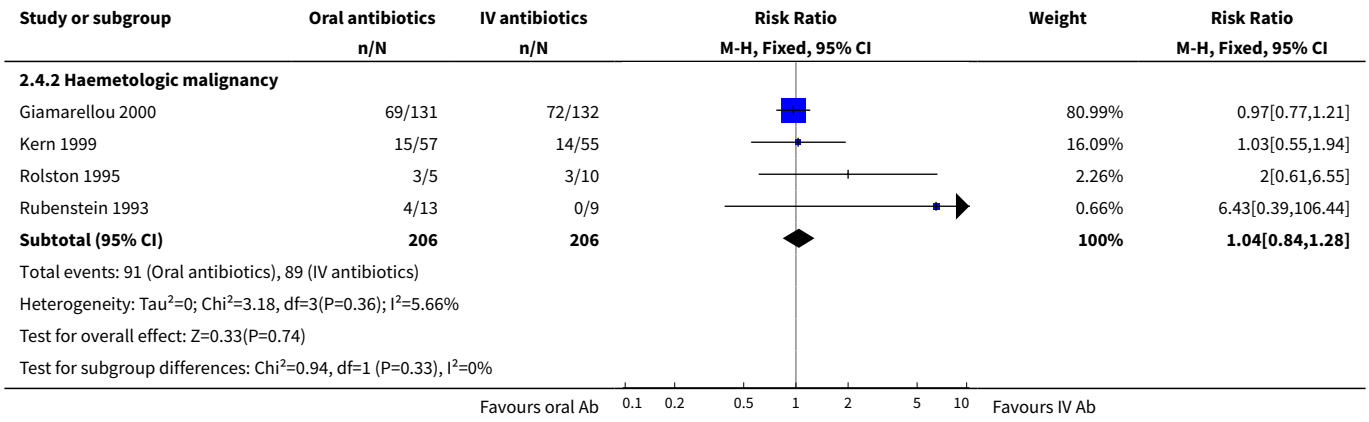


Analysis 2.3. Comparison 2 Oral versus intravenous antibiotic therapy - subgroup analysis, Outcome 3 Treatment failure - severity of neutropenia.



Analysis 2.4. Comparison 2 Oral versus intravenous antibiotic therapy - subgroup analysis, Outcome 4 Treatment failure - type of malignancy.

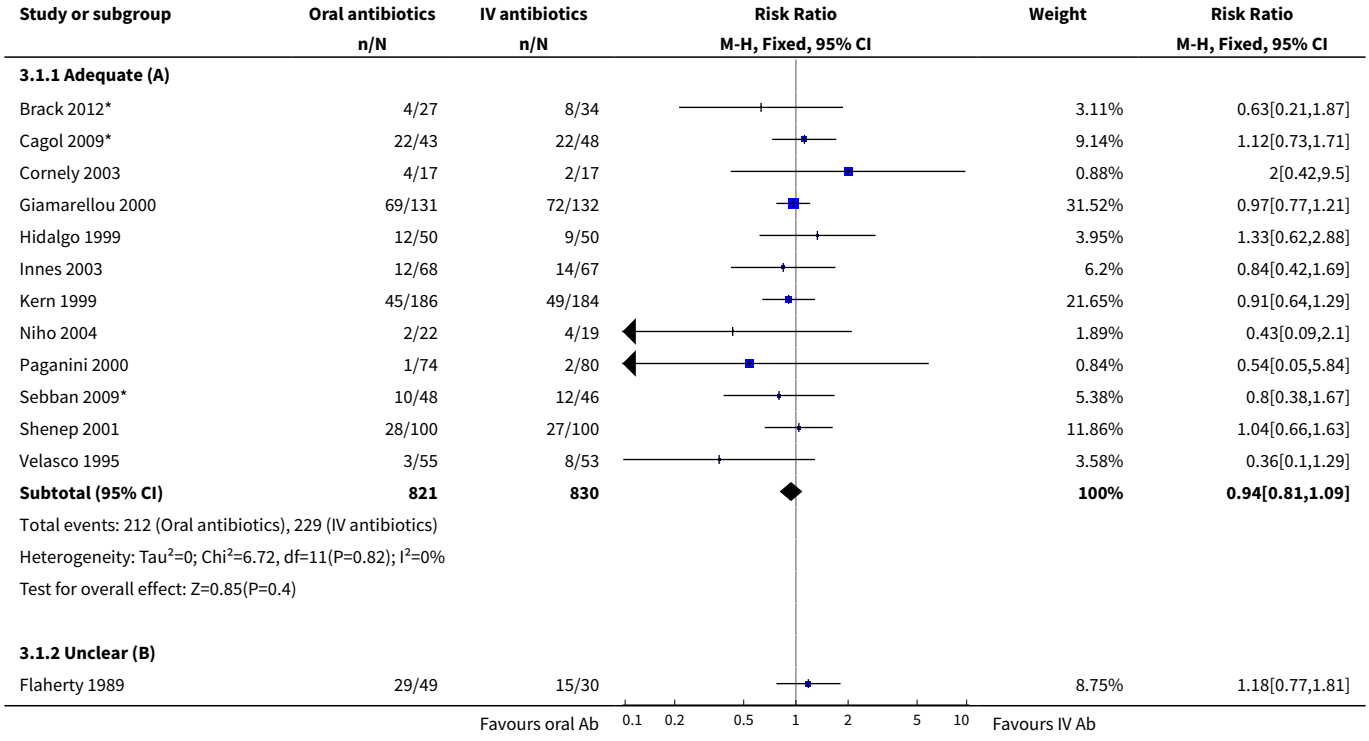


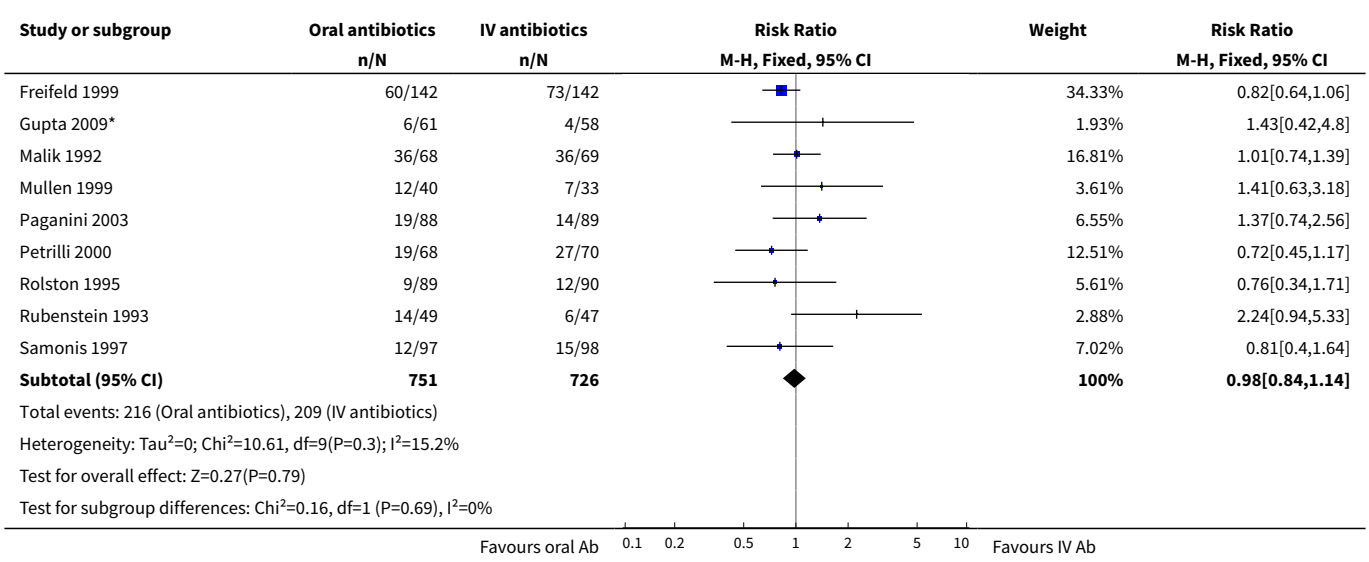


Comparison 3. Methodological quality of studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allocation concealment	22		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adequate (A)	12	1651	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
1.2 Unclear (B)	10	1477	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.14]

Analysis 3.1. Comparison 3 Methodological quality of studies, Outcome 1 Allocation concealment.



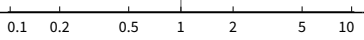


Comparison 4. Post hoc subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Setting	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oral-outpatient, IV-inpatients	3	430	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.63, 1.43]
1.2 Inpatients	6	1128	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.81, 1.07]
1.3 Outpatients	7	816	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.85, 1.50]
1.4 Only first dose in	2	161	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.41, 1.34]
2 Type of oral antibiotics	22		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Quinolones only	7	967	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.20]
2.2 Quinolones in combination with augmentin, ampicillin-sulbactam, penicillin V or clindamycin	11	1679	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
2.3 Cefixime	2	354	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.64, 1.56]
2.4 New quinolones	2	128	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.50, 1.86]

Analysis 4.1. Comparison 4 Post hoc subgroup analyses, Outcome 1 Setting.

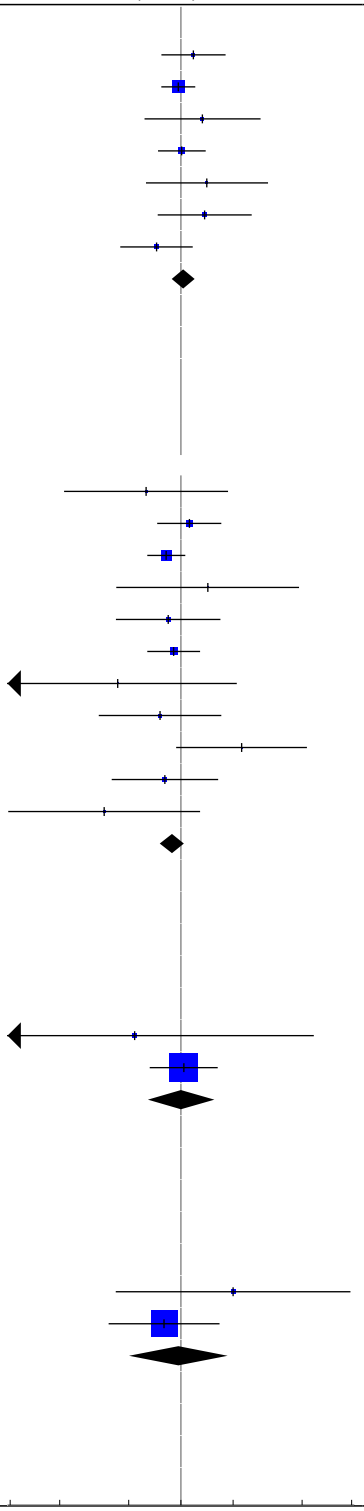
Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Oral-outpatient, IV-inpatients					
Hidalgo 1999	12/50	9/50		23.67%	1.33[0.62,2.88]
Innes 2003	12/68	14/67		37.09%	0.84[0.42,1.69]
Samonis 1997	12/97	15/98		39.24%	0.81[0.4,1.64]
Subtotal (95% CI)	**215**	**215**		**100%**	**0.95[0.63,1.43]**
Total events: 36 (Oral antibiotics), 38 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=1.06, df=2(P=0.59); I^2=0%					
Test for overall effect: Z=0.26(P=0.79)					
4.1.2 Inpatients					
Cagol 2009*	22/43	22/48		8.75%	1.12[0.73,1.71]
Flaherty 1989	29/49	15/30		7.83%	1.18[0.77,1.81]
Freifeld 1999	60/142	73/142		30.71%	0.82[0.64,1.06]
Giamarellou 2000	69/131	72/132		30.18%	0.97[0.77,1.21]
Kern 1999	45/186	49/184		20.73%	0.91[0.64,1.29]
Niho 2004	2/22	4/19		1.81%	0.43[0.09,2.1]
Subtotal (95% CI)	**573**	**555**		**100%**	**0.93[0.81,1.07]**
Total events: 227 (Oral antibiotics), 235 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=3.9, df=5(P=0.56); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					
4.1.3 Outpatients					
Cornely 2003	4/17	2/17		2.76%	2[0.42,9.5]
Gupta 2009*	6/61	4/58		5.67%	1.43[0.42,4.8]
Mullen 1999	12/40	7/33		10.6%	1.41[0.63,3.18]
Paganini 2003	19/88	14/89		19.24%	1.37[0.74,2.56]
Petrilli 2000	19/68	27/70		36.77%	0.72[0.45,1.17]
Rolston 1995	9/89	12/90		16.49%	0.76[0.34,1.71]
Rubenstein 1993	14/49	6/47		8.46%	2.24[0.94,5.33]
Subtotal (95% CI)	**412**	**404**		**100%**	**1.13[0.85,1.5]**
Total events: 83 (Oral antibiotics), 72 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=7.89, df=6(P=0.25); I^2=23.92%					
Test for overall effect: Z=0.86(P=0.39)					
4.1.4 Only first dose in					
Brack 2012*	5/33	8/34		39.14%	0.64[0.23,1.77]
Sebban 2009*	10/48	12/46		60.86%	0.8[0.38,1.67]
Subtotal (95% CI)	**81**	**80**		**100%**	**0.74[0.41,1.34]**
Total events: 15 (Oral antibiotics), 20 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%					
Test for overall effect: Z=1(P=0.32)					
Test for subgroup differences: Chi^2=2.26, df=1 (P=0.52), I^2=0%					



Favours oral Ab — Favours IV Ab

Analysis 4.2. Comparison 4 Post hoc subgroup analyses, Outcome 2 Type of oral antibiotics.

Study or subgroup	Oral antibiotics n/N	IV antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Quinolones only					
Flaherty 1989	29/49	15/30		10.15%	1.18[0.77,1.81]
Giamarellou 2000	69/131	72/132		39.14%	0.97[0.77,1.21]
Hidalgo 1999	12/50	9/50		4.91%	1.33[0.62,2.88]
Malik 1992	36/68	36/69		19.5%	1.01[0.74,1.39]
Mullen 1999	12/40	7/33		4.19%	1.41[0.63,3.18]
Paganini 2003	19/88	14/89		7.6%	1.37[0.74,2.56]
Petrilli 2000	19/68	27/70		14.52%	0.72[0.45,1.17]
Subtotal (95% CI)	**494**	**473**		**100%**	**1.03[0.88,1.2]**
Total events: 196 (Oral antibiotics), 180 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=4.61, df=6(P=0.6); I^2=0%					
Test for overall effect: Z=0.38(P=0.7)					
4.2.2 Quinolones in combination with augmentin, ampicillin-sulbactam, penicillin V or clindamycin					
Brack 2012*	4/27	8/34		3.31%	0.63[0.21,1.87]
Cagol 2009*	22/43	22/48		9.73%	1.12[0.73,1.71]
Freifeld 1999	60/142	73/142		34.15%	0.82[0.64,1.06]
Gupta 2009*	6/61	4/58		1.92%	1.43[0.42,4.8]
Innes 2003	12/68	14/67		6.6%	0.84[0.42,1.69]
Kern 1999	45/186	49/184		23.05%	0.91[0.64,1.29]
Niho 2004	2/22	4/19		2.01%	0.43[0.09,2.1]
Rolston 1995	9/89	12/90		5.58%	0.76[0.34,1.71]
Rubenstein 1993	14/49	6/47		2.87%	2.24[0.94,5.33]
Samonis 1997	12/97	15/98		6.98%	0.81[0.4,1.64]
Velasco 1995	3/55	8/53		3.81%	0.36[0.1,1.29]
Subtotal (95% CI)	**839**	**840**		**100%**	**0.89[0.76,1.04]**
Total events: 189 (Oral antibiotics), 215 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=9.77, df=10(P=0.46); I^2=0%					
Test for overall effect: Z=1.44(P=0.15)					
4.2.3 Cefixime					
Paganini 2000	1/74	2/80		6.65%	0.54[0.05,5.84]
Shenep 2001	28/100	27/100		93.35%	1.04[0.66,1.63]
Subtotal (95% CI)	**174**	**180**		**100%**	**1[0.64,1.56]**
Total events: 29 (Oral antibiotics), 29 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.02(P=0.99)					
4.2.4 New quinolones					
Cornely 2003	4/17	2/17		14.03%	2[0.42,9.5]
Sebban 2009*	10/48	12/46		85.97%	0.8[0.38,1.67]
Subtotal (95% CI)	**65**	**63**		**100%**	**0.97[0.5,1.86]**
Total events: 14 (Oral antibiotics), 14 (IV antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=1.1, df=1(P=0.3); I^2=8.7%					
Test for overall effect: Z=0.1(P=0.92)					
Test for subgroup differences: Chi^2=1.75, df=1 (P=0.63), I^2=0%					



ADDITIONAL TABLES

Table 1. Criteria for low risk patients (as defined in most included studies)

Common criteria
Haemodynamic stablity
No organ failure
Ability to take oral medications
No pneumonia
No infection of a central line
No severe soft-tissue infection
No acute leukaemia as the background malignancy
No known drug allergy
Not pregnant or lactating women

Table 2. Exclusion criteria of included trials (2004)

Study ID	Evident infection	Previous AB	Prolonged neutropeni	Performance status	Active malignancy	BMT/PSCT	Other
Kern 1999	Infected catheter or CNS infection, known bacterial /viral/fungal infection	yes	yes	no	no	yes	Need of IV supportive therapy, expected to die within 48 hours, HIV, fever unrelated to infection and protocol violation
Mullen 1999	A source of infection that required hospitalisation as: tunnelitis, pneumonia, perirectal cellulitis, typhlitis, resistant microorganism to one of the study's drugs	no	no	no	yes	yes	>10% dehydration, bleeding requiring platelet transfusion, need for IV access, no access to telephone, >1hour away from hospital unreliable caretaker
Paganini 2000	Infected catheter, perineal/ facial cellulitis, uncontrolled local infection, positive blood cultures at 72 hours	no	no	no	yes	yes	Persistance of fever >48 hours, incorrectable bleeding; refractory hypoglycemia or hypocalcemia
Rubenstein 1993	Known resistant microorganism	no	no	no	no	no	Na<128, uncontrolled hypercalcemia, more than 30 miles away
Samonis 1997	Pneumonia, deep organ infection	yes	yes	no	yes	no*	Prior hospitalisation
Shenep 2001	Pneumonia, clinical or radiographic evidence of focal bacterial infection, severe mucositis, positive blood cultures at 48 hours	no	no	no	no	no	MRSA or P.Aeroginosa in any culture obtained in preceding 12weeks
Velasco1995	Meningitis, pyelonephritis	yes	no	yes	no	no*	Long term central vein catheter
Petrilli 1999	no	no	no	no	no	no*	
Flaherty 1989	no	yes	no	no	no	no	
Freifeld 1999	Intravascular infection, tunnelitis, pneumonia, neurologic symtoms,	no	yes	no	no	yes	Treatment with Ca-Mg or probenecid or alluporinol or theophylline, HIV

Table 2. Exclusion criteria of included trials (2004) *(Continued)*

Giamarelou 2000	Suspected anaerobes	no	no	yes	no	no	Moribund and high probability of dying within 48 hours
Hidalgo 1999	Pneumonia, extensive cellulitis, meningitis, pyelonephritis	no	no	yes	yes	no	Clotting abnormalities, acidosis, hypercalcaemia, uncontrolled bleeding, live >2h apart from hospital; Hx of tumour fever, other severe extra hematologic chemotherapy induced toxicity, no 24 hours home companion
Innes 2003	Tunnelitis, cellulitis, abcess, clinically documented infection likely to require prolonged antibiotic therapy	yes	yes	no	no	yes	Need for the use of G/GM-CSF and cytokines; no responsible adult living with them (carer);
Malik 1992	no	yes	no	no	no	no	Recurrent FUO
Cornely 2003	not excluded	excluded (except cotrimoxazole prophylaxis)	yes	yes	excluded	excluded	potential compromised absorption; inability to take oral medication; tenopathy, epilepsy; aplastic anaemia, acute leukaemia; septic shock or signs of sever infection; HIV carrier; serious concomitant disease, liver transaminase> x5 of norm.
Niho 2004	not excluded	excluded	no	not excluded	no	yes	Recurrent FUO; renal insufficiency; hepatic insufficiency; hypotension or peripheral circulatory failure; uncontrolled hypercalcaemia; altered sensorium; respiratory rate >30 breaths/min; serum sodium <128 mg/dl; inability to take oral medications; intestinal malabsorption
Paganini 2003	Fascial, perineal, or catheter-associated cellulites; uncontrolled local infection; positive blood cultures within the first 48 hours; infection with microorganisms known as	included	yes	not excluded	not excluded	excluded	severe comorbidity factors; respiratory failure

Table 2. Exclusion criteria of included trials (2004) *(Continued)*

	resistant to ceftriaxone or ciprofloxacin

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Neutropenia, this term only
#2 neutrop* or granulo* or leukop*
#3 (#1 OR #2)
#4 MeSH descriptor Fever explode all trees
#5 MeSH descriptor Bacterial Infections explode all trees
#6 MeSH descriptor Sepsis explode all trees
#7 fever* or febrile or infect* or septic or sepsis
#8 (#4 OR #5 OR #6 OR #7)
#9 Any MeSH descriptor with qualifier: DT
#10 MeSH descriptor Anti-Infective Agents explode all trees
#11 antibiotic* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or antiinfect* or anti-infect*
#12 (#9 OR #10 OR #11)
#13 MeSH descriptor Drug Administration Routesexplode all trees
#14 oral* or per os or intravenous* or IV or parenteral*
#15 (#13 OR #14)
#16 MeSH descriptor Neoplasms explode all trees
#17 cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or lymphoma* or leukemia* or leukaemia* or myeloma*
#18 bone marrow and transplant*
#19 (#16 OR #17 OR #18)
#20 (#3 AND #8 AND #12 AND #15 AND #19)

Appendix 2. MEDLINE search strategy

1 Neutropenia/
2 (neutrop* or granulo* or leukop*).mp.
3 1 or 2
4 exp Fever/
5 exp Bacterial Infections/
6 exp Sepsis/
7 (fever* or febrile or infect* or sepsis or septic).mp.
8 4 or 5 or 6 or 7
9 drug therapy.fs.
10 exp Anti-Infective Agents/
11 (antibiotic* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or antiinfect* or anti-infect*).mp.
12 9 or 10 or 11
13 exp Drug Administration Routes/
14 (oral* or per os or intravenous* or IV or parenteral*).mp.
15 13 or 14
16 exp Neoplasms/
17 Bone Marrow Transplantation/
18 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or lymphoma* or leukemia* or leukaemia* or myeloma*).mp.
19 (bone marrow and transplant*).mp.
20 16 or 17 or 18 or 19
21 3 and 8 and 12 and 15 and 20
22 randomized controlled trial.pt.
23 controlled clinical trial.pt.
24 randomized.ab.
25 placebo.ab.
26 clinical trials as topic.sh.
27 randomly.ab.
28 trial.ti.
29 22 or 23 or 24 or 25 or 26 or 27 or 28
30 21 and 29

key:
mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
pt=publication type

ab=abstract
ti=title
sh=subject heading

Appendix 3. EMBASE search strategy

1 exp neutropenia/
2 (neutrop* or granulo* or leukop*).mp.
3 1 or 2
4 exp fever/
5 exp bacterial infection/
6 exp sepsis/
7 (fever* or febrile or infect* or septic or sepsis).mp.
8 4 or 5 or 6 or 7
9 exp antiinfective agent/
10 (antibiotic* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or antiinfect* or anti-infect*).mp.
11 9 or 10
12 exp drug administration route/
13 (oral* or per os or intravenous* or IV or parenteral*).mp.
14 12 or 13
15 exp neoplasm/
16 exp bone marrow transplantation/
17 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or lymphoma* or leukemia* or leukaemia* or myeloma*).mp.
18 (bone marrow and transplant*).mp.
19 15 or 16 or 17 or 18
20 3 and 8 and 11 and 14 and 19
21 crossover procedure/
22 randomized controlled trial/
23 single blind procedure/
24 random*.mp.
25 factorial*.mp.
26 (crossover* or cross over* or cross-over).mp.
27 placebo*.mp.
28 (doubl* adj blind*).mp.
29 (singl* adj blind*).mp.
30 assign*.mp.
31 allocat*.mp.
32 volunteer*.mp.
33 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 20 and 33

key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 4. LILACS search strategy

((fever*:ME OR febrile OR infection*:ME OR infect* OR sepsis*:ME) AND (neutropenia*:ME OR neutropen* OR neutropaen* OR granulocytopen* OR granulocytopaen* OR leukopen* OR leukopaen*) AND (oral OR per-os) AND (intravenous OR parenteral) AND ((antibiotics*:ME OR antibiot* OR antimicrob* OR anti-microb* OR antibact* OR anti infective agents*:ME) NOT decontamination*:ME))

WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 4, 2004

Date	Event	Description
11 February 2015	Amended	Contact details updated.
26 February 2014	Amended	Contact details updated.
22 August 2013	New citation required but conclusions have not changed	Four new studies added, conclusions unchanged
22 August 2013	New search has been performed	Literature searches updated in January 2013
12 November 2007	New search has been performed	Minor update: 12/11/07 New searches were conducted in September 2007. Three additional included trials were identified and added to this version of the updated review (Cornely 2003; Niho 2004; Paganini 2003).
9 August 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Liat Vidal (contact review author) - reference search, article retrieval, study inclusion and exclusion, data extraction, analysis, and writing.
Mical Paul - data extraction, study inclusion and exclusion, analysis, and manuscript review.
Itsik Ben dor - reference search, data extraction, study inclusion and exclusion.
Ellisheva Pokroy- reference search, article retrieval.
Karla Soares-Weiser - analysis, interpretation of results and manuscript review.
Leonard Leibovici (secondary contact) - study inclusion and exclusion, analysis, and manuscript review.

Noa Eliakim-Raz - reference search, data extraction, study inclusion and exclusion.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

NOTES

A version of this review was published in the Journal of Antimicrobial Chemotherapy 2004 Jul;54(1):29-37.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anti-Bacterial Agents [*administration & dosage] [adverse effects]; Chemotherapy-Induced Febrile Neutropenia [*drug therapy] [mortality]; Injections, Intravenous; Neoplasms [*drug therapy]; Randomized Controlled Trials as Topic; Treatment Failure

MeSH check words

Humans