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Design: Cochrane Systematic Review
Country: International

Aim: To compare the efficacy of intravenous (IV) antibiotic treatment to that of sequential IV-to-oral antibiotic treatment in patients with cancer and chemotherapy-induced neutropenia or patients with cancer who underwent a bonemarrow transplantation who presented with fever.

Inclusion criteria
Randomised controlled trials (RCTs) comparing any single or combination IV antibiotics to any single or combination sequential IV-to-oral antibiotics for the treatment of febrile neutropenia in cancer patients.

Exclusion criteria

Population
6 studies were included in the review:
Flaherty et al. (1989): N = 77 cancer patients with 86 episodes of fever and neutropenia; age range = 29-82 years; type of malignancy: Acute leukaemia (30%), Chronic leukemia (22%), lymphoma (6%), solid tumour (35%). USA 1988-89.
Giamarellou et al. (2000): N = 263 cancer patients with fever and neutropenia; mean age ≈ 54.4 (SD ≈ 17) years; all had with haematologic malignancies or aplastic anaemia. Greece 1992-95.
Mullen et al. (1999): N = 44 cancer patients with 76 episodes of fever and neutropenia; age range = 3-20 years; type of malignancy: Leukaemia (30%), non-leukemia (70%). USA 1995-97.
Paganini et al. (2000): N = 124 cancer patients with 154 episodes of fever and neutropenia; age range = 9 months-16.6 years; type of malignancy: Leukaemia (52%), lymphoma (5%), solid tumours (43%). Argentina 1997-98.
Paganini et al. (2003): N = 135 cancer patients with 177 episodes of fever and neutropenia; median age = 7.5 (range 1.6–15.8) years; type of malignancy: Acute leukaemia (59%), lymphoma (4%), solid tumours (37.5%). Argentina 2000-2002.
Shenep et al. (2001): N = 156 cancer patients with 200 episodes of fever and neutropenia; age range = 1.3–19) years; type of malignancy: Acute lymphoblastic leukaemia (53.5%), acute non-lymphoblastic leukemia (7%), solid tumours (38%), other leukemia or blood disorder (1.5%). USA 1991-1995.

Interventions
Flaherty et al. (1989): 3 regimens (as inpatients; episodes were randomised):
(1) Ciprofloxacin 300mg IV every 12 hours and azlocillin 4g IV every 6 hours with conversion to ciprofloxacin 750mg orally every 12 hours after 72 hours, if a favourable clinical and bacteriologic response to IV antibiotics had occurred and the patient was able to take oral medications;
(2) Ceftazidime 2g IV every 8 hours and amikacin 7.5mg/kg IV every 12 hours;
(3) Ceftazidime 2g IV every 8 hours and amikacin 7.5mg/kg IV every 12 hours with conversion to ciprofloxacin 750mg orally every 12 hours after 72 hours if clinical and bacteriologic response was appropriate.
Giamarellou et al. (2000): 2 regimens (as inpatients; patients were randomised):
(1) Ciprofluoxacin 400mg IV every 8 hours with conversion to oral ciprofluoxacin 750mg every 12 hours after 72 hours if successful response to IV antibiotics had occurred and the patients were able to tolerate oral medication.
(2) Ceftazidime 2g IV every 8 hours and amikacin 15 mg/kg of body weight/day IV over 30 min divided into two doses.

Mullen et al. (1999): 2 regimens (as outpatients; episodes were randomised):
(1) Single dose of ceftazidime 50mg/kg max 2g IV, change to oral ciprofluoxacin 12.5mg/kg every 12 hours.
(2) Ceftazidime 50mg/kg max 2g IV every 8 hours.
Paganini et al. (2000): 2 regimens (as outpatients; episodes were randomised):
(1) Ceftriaxone 100 mg/kg/day IV every 12 hours and amikacin IV 15 mg/kg/day every 24 hours) for 3 days, then conversion to oral cefixime 8 mg/kg/day every 24 hours for 4 days
(2) Ceftriaxone 100 mg/kg/day IV every 12 hours and amikacin IV 15 mg/kg/day every 24 hours) for 7 days.
Paganini et al. (2003): 2 regimens (as outpatients; episodes were randomised):
(1) Ceftriaxone 100 mg/kg per day as a single IV dose (maximum dose, 2 g) plus amikacin 15 mg/kg per day as a single IV dose the first day followed by ciprofloxacin 20 mg/kg per day orally every 12 hours,
(2) Ceftriaxone 100 mg/kg per day as a single IV dose (maximum dose, 2 g) plus amikacin 15 mg/kg per day as a single IV dose the first day followed by ceftriaxone 100mg/kg/day IV.
In both groups, antibiotic therapy was stopped when patients remained afebrile for 24 hours and the neutrophil count > 100/mm^3.
Shenep et al. (2001): 2 regimens (as inpatients; episodes were randomised):
(1) IV Tobramycin (or amikacin) + ticarcillin +vancomycin OR ceftazidime +vancomycin until randomisation after 48-72 hours and then change to oral cefixime suspension 4mg/kg every 12 hours.
(2) IV tobramycin every 6 hours 60mg/m^2 (or amikacin) + ticarcillin 2.25g/m^2 max 18g/day + vancomycin 300mg/m^2 max 4g/day or ceftazidime 1.5g/m^2 +vancomycin if renal failure or nephrotoxic chemotherapy.
All patients received prophylactic trimethoprim-sulfamethoxazole 150 mg/m^2 in 2 divided doses on 3 consecutive days each week.

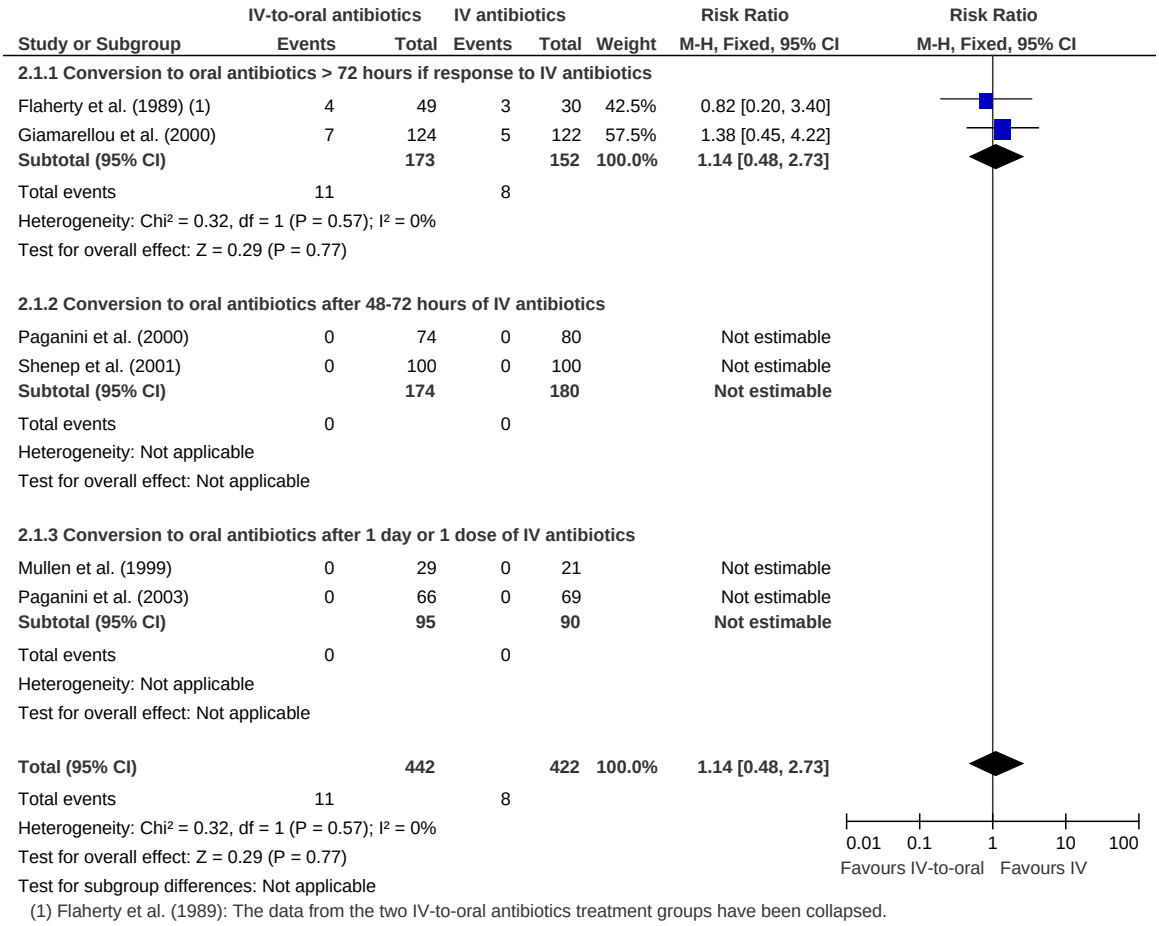
Outcomes

Vidal et al (2004; i.e., Cochrane review):
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). Treatment failure defined as a composite end-point 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.
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.
Flaherty et al. (1989): All cause mortality, treatment failure, number of patients who become afebrile, length of febrile episode, duration of therapy, adverse events (requiring discontinuation). Definitions of failure: any death prior to neutrophil recovery; addition of antibiotics (success with modification).
Giamarellou et al. (2000): All cause mortality, infection-related mortality, duration of therapy, adverse events (any, requiring discontinuation). Definitions of failure: Death due to infection, fever and/or pathogen did not respond necessitating a modification in the assigned regimen, clinical or microbiological relapse within 7 days after discontinuation, superinfection.
Mullen et al. (1999): All cause mortality, treatment failure, length of febrile episode, length of hospital stay, lost to follow up, adverse events (?-are all reported?). Definitions of failure: Hospitalisation for any reason (indications for admission: positive blood culture and > 3 days fever, > 5 days fever, emesis, hypersensitivity, life threatening treatment related complications, deterioration).
Paganini et al. (2000): 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. Definitions of failure: Re-admission due to recurrence of fever.
Paganini et al. (2003): All cause mortality, treatment failure, treatment failure not due to modification of the primary intervention, adverse events.
Shenep et al. (2001): All cause mortality, treatment failure, treatment failure not due to modification of the primary intervention, lost to follow up, adverse events requiring discontinuation. Definitions of 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.

Results

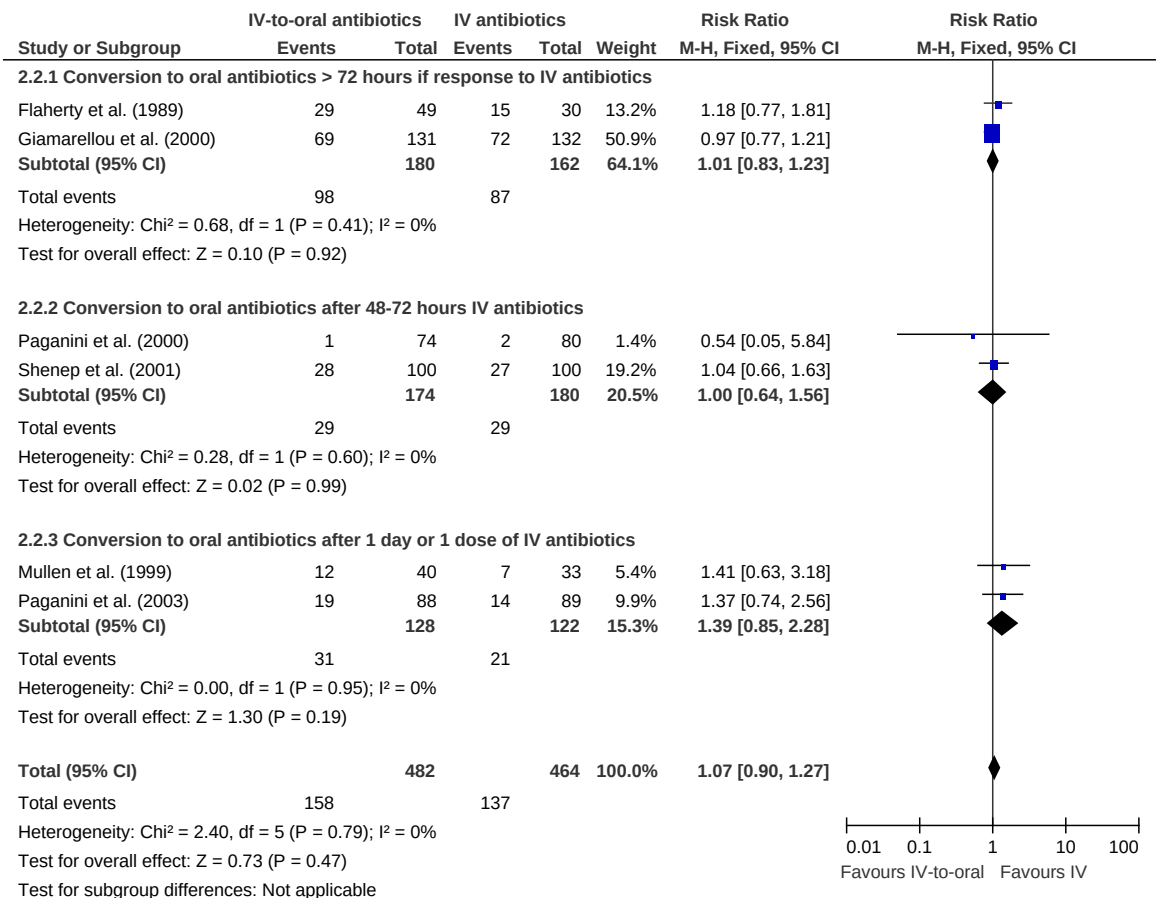
Mortality: Overall and by time of IV-to-oral switch:



(1) Flaherty et al. (1989): The data from the two IV-to-oral antibiotics treatment groups have been collapsed.

No deaths occurred in Mullen et al. (1999), Paganini et al. (2001, 2003) and Shenep et al. (2001). The risk of death did not differ between the patients who received IV antibiotics only and those patients who were switched from IV to oral antibiotics after 72 hours if they had responded to IV antibiotics (Flaherty et al., 1989; Giamarellou et al., 2000); Risk ratio = 1.14 (95% CI .48-2.73), p = .77, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure: Overall and by time of IV-to-oral switch:



The overall risk of treatment failure did not differ between the patients who received IV antibiotics only and those patients in the IV-to-oral antibiotics treatment groups (Risk ratio = 1.07 (95% CI .9-1.27), p = .47, I^2 = 0%, that is, there was no heterogeneity). The risk of treatment failure was also not found to differ between the treatment groups within the 3 'time of switch from IV to oral antibiotics' subgroups (see forest plot for individual subgroup risk ratios).

Vidal et al. (2004): Further meta-analyses:

Treatment failure (per protocol analysis): All 6 studies were included; total N = 470 in IV-to-oral group and 451 in IV group with 142 events in the IV-to-oral group and 122 events in the IV group; Risk ratio = 1.07 (95% CI .88-1.29), p = .51, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (children): Mullen et al. (1999), Paganini et al. (2000, 2003), and Shenep et al. (2001) were included; total N = 302 in IV-to-oral group and 302 in IV group with 60 events in the IV-to-oral group and 50 events in the IV group; Risk ratio = 1.17 (95% CI .84-1.62), p = .36, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (adults): Flaherty et al. (1989), and Giamarellou et al. (2000) were included; total N = 180 in IV-to-oral group and 162 in IV group with 98 events in the IV-to-oral group and 87 events in the IV group; Risk ratio = 1.01 (95% CI .83-1.23), p = .92, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (out-patients): Mullen et al. (1999), and Paganini et al. (2003) were included; total N = 128 in IV-to-oral group and 122 in IV group with 31 events in the IV-to-oral group and 21 events in the IV group; Risk ratio = 1.39 (95% CI .85-2.28), p = .19, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (in-patients): Flaherty et al. (1989), and Giamarellou et al. (2000) were included; total N = 180 in IV-to-oral group and 162 in IV group with 98 events in the IV-to-oral group and 87 events in the IV group; Risk ratio = 1.01 (95% CI .83-1.23), p = .92, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (quinolones only): Flaherty et al. (1989), Giamarellou et al. (2000), Mullen et al. (1999), and

Paganini et al. (2003) were included; total N = 308 in IV-to-oral group and 284 in IV group with 129 events in the IV-to-oral group and 108 events in the IV group; Risk ratio = 1.08 (95% CI .9-1.31), p = .41, I^2 = 0%, that is, there was no heterogeneity.
Treatment failure (cefixime): Paganini et al. (2000) and Shenep et al. (2001) were included; total N = 174 in IV-to-oral group and 180 in IV group with 29 events in the IV-to-oral group and 29 events in the IV group; Risk ratio = 1 (95% CI .64-1.56), p = .99, I^2 = 0%, that is, there was no heterogeneity.
Adverse events requiring discontinuation of antibiotics: All studies apart from Paganini et al. (2003) were included; total N = 389 in IV-to-oral group and 370 in IV group with 10 events in the IV-to-oral group and 13 events in the IV group; Risk ratio = .57 (95% CI .26-1.25), p = .16, I^2 = 0%, that is, there was no heterogeneity.
Gastrointestinal adverse events (post-protocol analysis): Included studies were Giamarellou et al. (2000), Paganini et al. (2000, 2003), Shenep et al. (2001); total N = 388 in IV-to-oral group and 396 in IV group with 14 events in the IV-to-oral group and 5 events in the IV group; Risk ratio = 2.81 (95% CI 1.03-7.66), p = .044, I^2 = 0%, that is, there was no heterogeneity. **The risk of experiencing gastrointestinal adverse events was 2.81 times higher for the patients in the IV-to-oral group compared to the patients in the IV group**.

Further results from the individual studies:
Flaherty et al. (1989):
Exclusions from analysis: 7/86 episodes of unknown treatment assignment.
Follow up period: End of fever and neutropenia.
Giamarellou et al. (2000):
Exclusions from analysis: 17/263 patients (no difference between treatment groups).
Follow up period: 7 days following end of antibiotic treatment.
Mullen et al. (1999):
Exclusions from analysis: 3/76 episodes of unknown treatment assignment.
Follow up period: End of antibiotic treatment.
The groups did not differ statistically significantly in duration of fever or treatment or in number of hospitalisations.
Paganini et al. (2000):
There were no exclusions from analysis.
Follow up period: 30 days following randomisation (which took place on day 3 of treatment).
The groups did not differ statistically significantly in duration of fever.
Paganini et al. (2003):
There were no exclusions from analysis.
Follow up period: Episode of fever and neutropenia, at least 7 days.
The groups did not differ statistically significantly in duration of fever and none of the patients required admission to the intensive care unit.
Shenep et al. (2001):
There were no exclusions from analysis.
Follow up period: End of antibiotic treatment.

General comments
The papers included in this systematic review have been comprehensively evaluated for bias and overall quality and are of varying quality (see next paragraph for further details about the quality of the included studies). Although no heterogeneity was evident in any of the analyses, the included studies used different patient populations (children and adults), different treatments and different times/criteria for switching from IV to oral antibiotics. These differences are likely to impact on the results and were therefore explored in subgroup analyses. However, only six studies were included in total and it is therefore unlikely that the subgroup analyses were sufficiently powered to detect any potential differences between the treatments and these must therefore be treated with caution.

Methodological features of the included studies:
Flaherty et al. (1989): No information about randomisation, allocation concealment, and blinding. Intention to treat analysis not used.
Giamarellou et al. (2000): No information about randomisation, adequate allocation concealment, and no blinding. Intention to treat analysis not used.
Mullen et al. (1999): No information about allocation concealment and blinding. Intention to treat analysis not used. Randomisation performed using a computer program.
Paganini et al. (2000): No information about blinding. Unclear whether allocation concealment was employed. Intention to treat analysis not used. Randomisation performed using a computer program.
Paganini et al. (2003): No blinding. Adequate allocation concealment. Intention to treat analysis was possibly used (episodes), but not explicitly reported. Randomisation performed using a computer program.
Shenep et al. (2001): Blinding of treatment providers. Adequate allocation concealment. Intention to treat analysis was used. Randomisation with stratification performed using a computer program.

References of Included Studies (For systematic reviews):
- Flaherty, J. P., Waitley, D., Edlin, B., George, D., Arnow, P., O'Keefe, P. et al. (1989). Multicenter, randomized trial of ciprofloxacin plus azlocillin versus ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. *American Journal of Medicine, 87,* 278S-282S.
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- Mullen, C. A., Petropoulos, D., Roberts, W. M., Rytting, M., Zipf, T., Chan, K. W. et al. (1999). Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer, 86,* 126-134.
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- Shenep, J. L., Flynn, P. M., Baker, D. K., Hetherington, S. V., Hudson, M. M., Hughes, W. T. et al. (2001). Oral cefixime is similar to continued intravenous antibiotics in the empirical treatment of febrile neutropenic children with cancer. *Clinical Infectious Diseases, 32,* 36-43.