Reference: Paul M, Grozinsky S, Soares-Weiser K, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database of Systematic Reviews: Reviews. Cochrane Database of Systematic Reviews 2006 Issue 1.Chichester (UK): John Wiley & Sons, Ltd; 2006.
Design: Systematic review (Cochrane Review) **Country**: Israel **Aim**: To compare beta-lactam monotherapy with beta-lactam-aminoglycoside therapy combination therapy for cancer patients with fever and neutropenia.
Inclusion criteria: Randomised or quasi randomised trials comparing any beta-lactam antibiotic monotherapy to any combination of a beta-lactam and aminoglycoside antibiotic. Allocation to either regimen had to occur initially (before administration of any other types of antibiotic for that neutropenic episode) and empirically (prior to detection of pathogens or their susceptibilities).
Exclusion criteria: Trials which randomised patients with microbiologically documented infections and trials comparing short versus long course of aminoglycoside were excluded – because in both cases treatment was not fully empirical. Trials in neonates and pre-term babies were excluded.
Population Cancer patients with febrile neutropenia (as defined in the primary studies) following chemotherapy or bone marrow transplantation.
Interventions Intravenous beta-lactam antibiotic given as monotherapy. This included: • Anti-pseudomonal carboxy-penicillins or ureido-penicillins with or without beta-lacatamase inhibitor • Cephalosporins

- Carbapenems

Combination duotherapy of an intravenous beta-lactam (see above) with one of the following aminoglycosides:

- Gentamicin, tobramycin, amikacin, netilmicin or kanamycin.

Outcomes

The primary outcome was all cause mortality, defined as death within the first 30 days of follow-up for the infectious episode.

Adverse events were categorised as: any adverse event, discontinuation due to adverse event, any nephrotoxicity and severe nephrotoxicity.

Secondary outcomes:

- Treatment failure, defined as at least one of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any modification of the assigned empirical antibiotic treatment.
- Infection related mortality,
- Duration of hospital stay,
- Dropouts before the end of the study,
- Superinfection, defined as new persistent or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen of the development of a new site of infection
- Colonisation: isolation during or following therapy of Gram-negative bacteria resistant to the beta-lactam included in the empiric regimen, with or without symptoms or signs of infection.

Results

Effectiveness

Outcome	Subgroup	N studies	N participants	Statistical method for meta-analysis	Effect size (less than 1 favours monotherapy)
All cause mortality	All	43	7114	Risk ratio, fixed effects model, 95% C.I.	0.87 [0.75 to 1.02]
	Same beta-lactam*	10	1646	Risk ratio, fixed effects model, 95% C.I.	0.74 [0.53 to 1.06]
	Different beta-lactam	33	5468	Risk ratio, fixed effects model, 95% C.I.	0.91 [0.77 to 1.09]
Infection related mortality	All	38	6656	Risk ratio, fixed effects model, 95% C.I.	0.80 [0.64 to 0.99]
	Same beta-lactam*	7	1331	Risk ratio, fixed effects model, 95% C.I.	0.68 [0.43 to 1.10]
	Different beta-lactam*	31	5325	Risk ratio, fixed effects model, 95% C.I.	0.83 [0.65 to 1.06]
Treatment failure	All	68	10285	Not reported	Not reported
	Same beta-lactam*	15	2761	Risk ratio, fixed effects model, 95%	1.11 [1.02 to 1.21]

				C.I.	
	Different beta-lactam*	53	7524	Risk ratio, fixed effects model, 95% C.I.	0.92 [0.87 to 0.96]

*Trials where the same beta-lactam was given in both arms of the trial.

Subgroup analysis of mortality and treatment failure was also done for the following groups: documented infections, bacteraemia, Gram-negative infections, pseudomonas infections, haematological cancer patients, those with severe neutropenia, monotherapy regimen and adults versus children. Sensitivity analyses of mortality and treatment failure was done for various indicators of trial quality.

Adverse events

Outcome	N studies	N participants	Statistical method for meta-analysis	Effect size (less than 1 favours monotherapy)
Any adverse event	47	7215	Risk ratio, fixed effects model, 95% C.I.	0.86 [0.80 to 0.93]
Discontinuation due to adverse event	16	4051	Risk ratio, fixed effects model, 95% C.I.	0.61 [0.40 to 0.93]
Any nephrotoxicity	37	6411	Risk ratio, fixed effects model, 95% C.I.	0.45 [0.35 to 0.57]
Severe nephtotoxicity	18	4002	Risk ratio, fixed effects model, 95% C.I.	0.16 [0.05 to 0.49]

Subgroup analyses of any-adverse-event was also done according to the specific drug used for monotherapy. Subgroup analysis of nephrotoxicity was also done for aminoglycoside dosing regimen (once daily versus multiple daily).

Superinfections

Outcome	N studies	N participants	Statistical method for meta-analysis	Effect size (less than 1 favours monotherapy)
Bacterial superinfection	28	4836	Risk ratio, fixed effects model, 95% C.I.	1.00 [0.86 to 1.18]
Fungal superinfection	20	3437	Risk ratio, fixed effects model, 95% C.I.	0.70 [0.49 to 1.00]

Colonisation of resistant Gram-negative bacteria

Five trials reported data about any colonisation but comparison between groups of colonisation with resistant Gram-negative bacteria was only possible in two trials. Resistant Gram-negative bacteria were detected in 5/152 patients treated with monotherapy versus 1/152 in those treated with combination therapy.

Duration of hospital stay

Three trials reported this outcome, in each one the duration of hospital stay was shorter (but not statistically significantly) in the monotherapy group. Data were not pooled due to the different ways in which the trials reported hospital stay.

Reference Pereira CA, Petrilli AS, Carlesse FA, Luisi FA, da Silva KV, de Martino Lee ML. - Cefepime monotherapy is as effective as ceftriaxone plus amikacin in pediatric patients with cancer and high-risk febrile neutropenia in a randomized comparison. - Journal of Microbiology, Immunology & Infection 2009 Apr;42(2):141-7.

Study type Randomised controlled trial. **Country** Brazil

Study quality
Randomisation: "based on number lists" no further details (unclear allocation concealment). Unit of randomisation was the episode of febrile neutropenia.
Blinding: none
Intention to treat: possible
Exclusions from analysis: None reported

Number of patients 57 patients (125 febrile neutropenic episodes). Patients were randomised at the start of each neutropenic episode. Some analyses are reported according to patient and some according to neutropenic episode.

Patient characteristics Children and adolescents (0 to 21 years) with acute leukemia or stage III and IV Hodgkin and non-Hodgkin lymphomas, who were considered to be at high risk of infectious complications following admission to hospital for febrile neutropenia. Neutropenia was defined as an absolute neutrophil count <500 cells/mm^3 or <1000 cells/mm^3 before the nadir of chemotherapy. Fever was defined as an axillary temperature above 38°C or 3 measurements 37.5°C or more during a 24 hour period.
Approximately half the patients had indwelling catheters.

Intervention Cefepime monotherapy, administered at a dose of 150 mg/kg/day given three times daily. All drugs were given intravenously. Therapy was modified with the inclusion of new antibacterial or antifungal agents according to the patients' clinical status, development of clinically or microbiologically documented infection or persistence of fever.

Comparison Ceftriaxone plus amikacin. Ceftriaxone was administered at a dose of 100 mg/kg/day given twice daily. Amikacin was given at a dose of 15mg/kg/day. Therapy was modified as above.

Length of follow-up The length of follow up was not reported**.** Patients were treated for a minimum of 5 days. The average time of treatment with antibiotics was 11.1 days (range 3 to 30 days) for monotherapy and 9.7 days (range 3 to 24 days) in the dual therapy group.

Outcome measures and effect size

Outcome	Monotherapy		Dual therapy		RR [95% C.I.]*
	n	N	n	N	
Treatment failure (for first FN episode)	10	29	10	28	0.97 [0.48, 1.96]
Mortality due to any cause (during the first FN episode)	1	29	1	28	0.97 [0.06, 14.70]
Any adverse event (per episode)	10	62	11	63	0.92 [0.42, 2.02]
Secondary infection (per episode, defined as any infection occurring between 72 hours after treatment started and 1 week after discontinuation of antibiotics). It was not stated whether it was bacterial or fungal infection (assumed bacterial).	14	62	10	63	1.42 [0.68, 2.96]

*Relative risk (RR) less than 1 favours monotherapy

54 pathogens were isolated from 125 episodes of febrile netropenia but Gram-negative bacterial resistance was not reported according to empirical therapy group (one strain of Pseudomonas aeruginosa was resistant

to ceftriaxone plus amikacin). Nephrotoxicity and quality of life were not reported.
Source of funding Not reported
General comments Need to check whether cefepime is used as monotherapy in the UK.

Reference Yildirim I, Aytac S, Ceyhan M, Cetin M, Tuncer M, Cengiz AB, et al. - Piperacillin/tazobactam plus amikacin versus carbapenem monotherapy as empirical treatment of febrile neutropenia in childhood hematological malignancies. - Pediatric Hematology & Oncology 2008 Jun;25(4):291-9.

Study type Randomised controlled trial **Country** Turkey

Study quality
Randomisation: Computer generated random number sequence –no further details (unclear allocation concealment). Unit of randomisation was the patient.
Blinding: none
Intention to treat: no
Exclusions from analysis: 12 patients with protocol violations were excluded from the study

Number of patients 99 patients were randomised, 87 were included in the analysis (12 were excluded for protocol violations: 4 in the dual therapy group and 8 in the monotherapy group).

Patient characteristics Patients aged 2 to 16 years with acute lymphoblastic leukaemia (N=69) or acute myeloblastic leukaemia (N=18) and neutropenic fever. Neutropenia was defined as absolute neutrophil count of ≤500 cells/mm^3 (or ≤1000 cells/mm^3 and predicted to be ≤500 cells/mm^3 within 24 hours). Fever was defined as body temperature of ≥38.5°C or at least two measurements ≥38.5°C within 24 hours. Only the first episode of febrile neutropenia was included in the analysis.
Approximately 90% of patients had a central venous catheter and G-CSF usage was 63% in both treatment groups.

Intervention Monotherapy with imipenem or meropenem (20 mg/kg three times a day). If the patient still had fever after 72 hours of empirical therapy a glycopeptide and amikacin was added to the original empirical carbapenem. The treatment was modified if results of culture or antiobiograms were positive.

Comparison Dual therapy with piperacillin/tazobactam (80 mg/kg piperacillin 10 mg/kg tazobactam four times a day) combined with amikacin (7.5 mg/kg twice a day). If the patient still had fever after 72 hours of empirical therapy a glycopeptide was added to the original empirical therapy. The treatment was modified if results of culture or antiobiograms were positive.

Length of follow-up The minimum duration of treatment was 7 days, with at least 4 days without fever. Clinical and biological documented infections were treated as long as necessary.

Outcome measures and effect size

Outcome	Monotherapy		Dual therapy		RR [95% C.I.]*
	n	N	n	N	
Treatment failure (defined as death due to infection, persistence of bacteraemia or documented breakthrough bacteraemia, or fever still persisting after 72 hours and prompting modification of initial treatment).	22	41	26	46	0.95 [0.65, 1.39]
Infection related mortality	0	41	0	46	Not estimable

*Relative risk (RR) less than 1 favours monotherapy

Duration of fever
The mean (S.D.) duration of fever was 5.9 days (4.8 days) for the carbapenem monotherapy group and 4.3 days (3.1 days) for the dual therapy group (P=0.06).

Duration of hospital stay
The mean (S.D.) hospital stay was 12.6 days (5.3 days) for the monotherapy group and 10.6 days (4.7 days) for the dual therapy group (P=0.06).

Bacterial resistance
20 cultures (in 19 patients) from 87 episodes of febrile neutropenia were positive for bacteria. These isolates were tested for resistance to the various antibiotics used in the trial but results were not reported according to empirical therapy group.

Source of funding Not reported

Reference Zengin E, Sarper N, and Kilic C. Piperacillin/Tazobactam Monotherapy Versus Piperacillin/Tazobactam Plus amikacin as Initial Empricial Therapy for Febrile Neutropenia in Children with Acute Leukemia. Pediatric Hematology and Oncology 2011. 28: 311 – 320.

Study type Randomised controlled trial **Country** Turkey **Study period** 2007 – 2008

Study quality
Randomisation: randomisation method and allocation concealment not reported (authors mention consecutive randomisation). It appears patients were randomised per febrile neutropenia episode (thus the same patient could be randomised more than once).
Blinding: not mentioned
Intention to treat: probably not (see below)
Exclusions from analysis: patients were excluded for protocol violation

Number of patients

Patient characteristics 42 patients aged up to 19 years with acute lymphoblastic leukaemia (N=60 episodes) or acute myeloblastic leukaemia (N=12 episodes) and neutropenic fever. Neutropenia was defined as absolute neutrophil count of ≤500 cells/mm^3 (or ≤1000 cells/mm^3 and predicted to be ≤500 cells/mm^3 within 24 hours). Fever was defined as body temperature of ≥38.5°C or ≥38°C for at least an hour. Multiple episodes of febrile neutropenia were eligible for inclusion.

Characteristic	PIP/TAZO	PIP/TAZO +amikacin
Median age (years) (range)	4.7 (0.4 to 19)	4.5 (1.56 to 19)
ALL	29	31
AML	8	4
CVC	65.3%	67.6%

Exclusion criteria: fever due to leukaemia or transfused drugs/blood products, history of hypersensitivity to trial drugs,

Intervention Piperacillin/tazobactam (PIP/TAZO) 360 mb/kg/day in 4 doses

Comparison Piperacillin/tazobactam (PIP/TAZO) 360 mb/kg/day in 4 doses plus amikacin 15/mg/kg/day in a single dose

Length of follow-up Patients were follow up for the duration of the neutropenic episode (up to 37 days).

Outcome measures and effect size

Outcome	Pip/Tazo		Pip/Tazo + amikacin		RR
	n	N	n	N	

Treatment success without modification (addition of teicoplanin, antifungal or antiviral)	17	37	15	35	
Treatment success with modification	13	37	13	35	
Protocol failure (change from empirical antibiotics in unresponsive fever)	7	37	7	35	
Glycopeptide addition	16	37	13	35	
Antifungal addition	9	37	5	35	
Infection related death	0	37	0	35	
Serious adverse events	0	37	0	35	
Median duration of fever (days) (range)	2 (1 to 13)		2 (1 to 19)		
Median duration of neutropenia (days) (range)	10 (3 to 32)		12 (1 to 37)		
Median duration of treatment (days) (range)	10 (5 to 31)		12 (4 to 30)		

Source of funding Not reported. The authors reported no conflicts of interest.