EJC SUPPLEMENTS 5 (2007) 13–22

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

The need for aminoglycosides in combination with β-lactams for high-risk, febrile neutropaenic patients with leukaemia ☆

Lubos Drgona [a], *Mical Paul* [b,*], *Giampaolo Bucaneve* [c], *Thierry Calandra* [d], *Francesco Menichetti* [e]

[a]*Department of Internal Medicine, National Cancer Institute, Bratislava, Slovakia*
[b]*Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel*
[c]*Department of Internal Medicine, Ospedale Silvestrini, Perugia, Italy*
[d]*Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, CH-1011 Lausanne, Switzerland*
[e]*Infectious Diseases Unit, Ospedale Cisanello, Pisa, Italy*

ARTICLE INFO

Article history:
Received 14 May 2007
Received in revised form 6 June 2007
Accepted 11 June 2007

Keywords:
Febrile neutropaenia
Monotherapy
Combination therapy
Aminoglycoside
Acute leukaemia

ABSTRACT

The efficacy and safety of aminoglycosides given in combination with β-lactams for the treatment of febrile neutropaenia in patients with acute leukaemia or bone marrow transplantation was assessed using an evidence-based review of the literature with the aim to formulate treatment guidelines. These recommendations have been developed by an expert panel of the European Conference on Infections in Leukaemic patients (ECIL-1). We also present results of a questionnaire on current treatment practice in Europe. The expert panel concluded that β-lactam monotherapy is as efficacious as and less toxic than β-lactam-aminoglycoside combination therapy as empirical therapy. The choice of β-lactam should be based on local epidemiological data, antibiotic resistance patterns, recent β-lactam use and available evidence. Combination therapy should be reserved for patients presenting with severe sepsis or septic shock or for those with a high suspicion of resistant Gram-negative infections, pending susceptibility testing and institution of appropriate β-lactam monotherapy.

1. Introduction

Early, broad-spectrum empirical antibiotic treatment for febrile neutropaenic patients has markedly reduced the mortality of Gram-negative infections.[1,2] For about two decades, combinations of an anti-pseudomonal β-lactam antibiotic with an aminoglycoside have been a gold standard for empirical therapy of suspected infections in febrile neutropaenic patients.[3,4] The rationale for combination therapy included broad-spectrum coverage, possible synergistic activity against Gram-negative bacteria (especially *Pseudomonas aeruginosa*) and the prevention of emergence of antibiotic resistance. Since the

☆ The ECIL-1 is a common initiative of the following groups or organizations: Infectious Diseases Working Party of the European Blood and Marrow Transplantation Group (EBMT-IDWP), Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), European Leukaemia, Net (ELN) (EU Grant number: LSHC-CT-2004), and International Immunocompromised Host Society (ICHS).

* *Corresponding author:* Tel.: +972 3 9376504; fax: +972 3 9376512.
E-mail address: pil1pel@zahav.net.il (M. Paul).

1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2007.06.003

early 1990s, several well-designed, randomised controlled trials have shown that monotherapy with broad-spectrum third- and fourth-generation cephalosporins (ceftazidime, cefpirome and cefepime), carbapenems (imipenem-cilastatin, meropenem) or anti-pseudomonal penicillins combined with an inhibitor of β-lactamases (piperacillin-tazobactam) was as efficacious as and less nephrotoxic or ototoxic than standard β-lactam-aminoglycoside combinations.

Until a few years ago, the management of cancer patients with febrile neutropaenia was fairly uniform. Recent advances in the treatment of cancer and management of chemotherapy-related complications have led to the recognition that all febrile neutropaenic patients are not at the same risk of infectious complications. Several factors can be used to classify patients into low or high risk categories.[5,6] Assessing whether the patient belongs to a low risk or high risk group is important; indeed, while low-risk patients may nowadays be safely treated with oral antibiotics,[7] high-risk patients should continue to receive intravenous broad-spectrum antibiotics. Patients with acute leukaemia, who are the focus of the present guidelines, are generally considered as high-risk patients.

With the advent of broad-spectrum and highly bactericidal β-lactam antibiotics and the shift from Gram-negative bacilli to Gram-positive cocci as the predominant cause of infections in neutropaenic cancer patients in the late 1980s and early 1990s,[8] the need for using an aminoglycoside in the empirical antibiotic regimen was a matter of considerable debate. The objective of the present article was to review the evidence supporting the use of aminoglycosides for managing bacterial infections in febrile neutropaenia. The literature was reviewed with the aim to answer the following questions:

(1) Is β-lactam monotherapy as efficacious as a combination of a β-lactam plus an aminoglycoside for upfront empirical therapy in high-risk febrile neutropaenic patients?
(2) Is a combination of a β-lactam plus an aminoglycoside more nephrotoxic or ototoxic than β-lactam monotherapy?
(3) Is there evidence that once-daily dosing of aminoglycosides is as efficacious as and potentially less toxic than multiple-daily dosing in febrile neutropaenic patients?
(4) Is there evidence supporting the empirical addition of an aminoglycoside to patients initially treated with monotherapy with persistent fever?
(5) Are there specific clinical conditions justifying the use of an aminoglycoside as part of the empirical antibiotic regimen?
(6) Does the use of β-lactam-aminoglycoside combinations in neutropaenic patients prevent the emergence of bacterial resistance?

2. Materials and methods

The Cochrane Library (September 2005) and Medline (January 1980 to September 2005) were used to search articles. Abstracts presented between 2002 and 2005 at annual meetings of the American Society of Haematology (ASH), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the American Society of Clinical Oncology (ASCO) and the European Bone Marrow Transplantation (EBMT) were also evaluated. References of all included trials and reviews were also checked. Databases were searched using the terms 'neutropaenia' or 'agranulocytosis' and similar; 'anti-infective agents' (including antibacterial and antibiotics); 'clinical trial' and similar; and 'aminoglycosides' or 'gentamicin', 'kanamycin', 'amikacin', 'tobramycin' and 'netilmicin'. Selection of relevant articles and abstracts was performed independently by two of the investigators (LD, FM and MP), crosschecked and approved by members of the study group (Fig. 1). Disagreements were resolved by consensus. All randomised controlled trials comparing β-lactam antibiotic monotherapy versus β-lactam–aminoglycoside combination therapy in adult neutropaenic cancer patients with acute leukaemia and meta-analyses comparing these regimens in neutropaenic cancer patients were included in this review. In addition, we included randomised controlled trials and meta-analyses comparing once daily versus multiple daily aminoglycoside dosing schedules in neutropaenic patients. The quality of the evidence and levels of recommendations were graded according to CDC criteria.[9] The endpoints assessed included all-cause mortality, treatment failure as defined in the primary data source, adverse events and infection-related mortality.

3. Results

3.1. *Questionnaire*

The ECIL panel of experts (37 responders) preferred monotherapy for the initial, empirical treatment of febrile neutropaenia (71.2%) and they favour the use of piperacillin/tazobactam (21%), meropenem (16%), imipenem (14.5%), cefepime (13.2 %) and ceftazidime (7%). Less than one-third of responders use β-lactam–aminoglycoside combinations for empirical antibiotic therapy. Twenty-two respondents indicated they would add an aminoglycoside for severe sepsis (29%), suspected *Pseudomonas* infection or resistant Gram-negative infection (26%), secondary infection (10%) and pneumonia (5%). The preferred aminoglycoside for the initial or second-line therapy was amikacin (69%) followed by gentamicin (19%). The duration of aminoglycoside therapy was extremely variable: ranging from 1 to 10–14 days or lasting until recovery of neutropaenia.

4. Review of the literature

4.1. *β-Lactam monotherapy versus β-lactam–aminoglycoside combination therapy*

Seventy-five randomised controlled trials and two meta-analyses comparing β-lactam monotherapy versus β-lactam–aminoglycoside combination therapy for febrile neutropaenia were identified. The two meta-analyses, which included 66

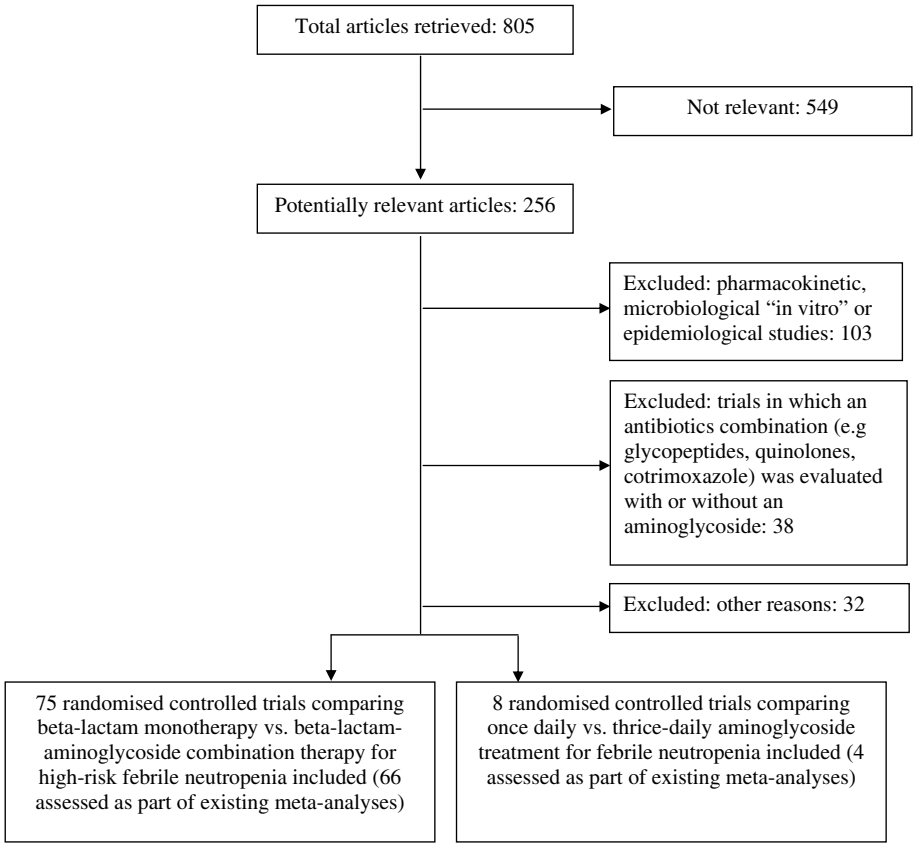

Fig. 1 – Study flow chart.

of the 75 trials identified, served as the main source of data for the present review.[10,11] The remaining nine trials were assessed separately.[12–20] Fifteen further studies, published mainly as abstracts at international meeting, were also evaluated. However, they were not retained in the final analysis for the following reasons: only children included,[21–28] only solid tumour patients included,[29,30] non-randomised trials,[31–34] no comparison between monotherapy and combination therapy[35] and one trial that included both neutropaenic and non-neutropaenic patients.[36]

4.2. *Meta-analysis 1*

The first meta-analysis by Paul et al. was performed as a Cochrane systematic review and published in 2002.[10] Forty-six randomised controlled trials (including 7642 patients) comparing monotherapy with any β-lactam antibiotic to any combination of a β-lactam and an aminoglycoside for the initial empirical treatment of febrile neutropaenic cancer patients were evaluated. The studies were performed between 1981 and 1999. The same β-lactam was used in both study arms in only 9 trials and different β-lactam antibiotics were used in the two study arms in 37 trials, consisting of a broad spectrum β-lactam compared to a narrower-spectrum β-lactam combined with an aminoglycoside. The β-lactams assessed for monotherapy included ceftazidime (14 trials), imipenem (14 trials, including a 2-armed trial), meropenem (6 trials), moxalactam (4 trials), piperacillin/tazobactam (3 trials), cefepime (2 trials) and cefoperazone, ceftriaxone, latamoxef and piperacillin (one trial each). Neutropaenia was defined as a neutrophil count of less than 0.5×10^9/L (500/mm^3) in half of the studies and less than 1.0×10^9/L (1000/mm^3) in the remainder. Bacteraemia was documented in 1874 patients. Microbiologically defined infections due to Gram-negative bacilli accounted for 12% (4–59%) of all treatment episodes and *P. aeruginosa* for less than 2% (0–13%) of episodes.

The study endpoints were analysed overall and in six subgroups: patients with underlying haematological malignancy or bone marrow transplantation, patients with an absolute granulocyte count of less than 0.1×10^9/L (100/mm^3), patients with bacteraemia, patients with microbiologically or clinically defined infections, patients with documented Gram-negative infections and patients with documented *Pseudomonas* infections.

The primary end-point was all-cause mortality defined as death at the end of follow-up for the infectious episode, up to 30 days. It was assessed in 29 studies. The average mortality rate was 6.2% (1.2–30%) with a mortality decline correlating with the year of the study. No significant difference between monotherapy and combination therapy was detected for all cause mortality (including in the six subgroups analysed). The overall relative risk of death was 0.85 (95% confidence interval 0.72–1.02) (favouring monotherapy, Table 1). The same results were obtained when the analysis was performed separately in the trials in which the same β-lactam

Table 1 – Summary of the main results of the two meta-analyses comparing beta-lactam monotherapy to β-lactam-aminoglycoside combination therapy for empirical therapy of febrile neutropaenia

	Paul et al. [10] 47 trials, 7807 patients, 8803 febrile episodes	Furno et al. [11] 29 trials, 4795 febrile episodes
All cause mortality		
•All studies	RR 0.85 CI 0.72–1.02	
•Studies using same β-lactam in both treatment arms	RR 0.73 CI 0.49–1.08	
Infection-related mortality		
•All studies	RR 0.76 CI 0.59–0.98	
•Studies using same β-lactam in both treatment arms	RR 0.72 CI 0.42–1.23	
Treatment failure		
•All studies	RR 0.91 CI 0.85-0.99	OR 0.88 CI 0.78–0.99
•Studies using same β-lactam in both treatment arms	RR 1.12 CI 0.96-1.29	
Bacteraemia	RR 0.69 CI 0.39–1.22 for mortality RR 0.91 CI 0.80–1.04 for failure	OR 0.70 CI 0.54–0.92 for failure
Superinfections	RR 0.97 CI 0.82–1.14 (bacterial superinfections) RR 0.75 CI 0.51–1.09 (fungal superinfections)	
Adverse events[a]	RR 0.57 CI 0.36–0.91	
Nephrotoxicity	RR 0.42 CI 0.32–0.56	

a Adverse events requiring discontinuation of antibiotic treatment. Relative risks (RR) or odds ratios (OR) with 95% confidence intervals (CI) for the comparison of β-lactam monotherapy versus β-lactam-aminoglycoside combination therapy. Values <1 favour monotherapy.

had been used ($n = 5$) or not ($n = 24$) in the two treatment arms (Table 1).

One of the secondary endpoints, treatment failure, was a composite end-point of one or more of the following: death, persistence of infection, recurrence or worsening of clinical signs and symptoms of presenting infection, or any modification of the initial empirical antibiotic treatment. There was no difference between monotherapy and combination therapy with respect to treatment failure in the nine studies (including 2178 episodes of neutropaenia) in which the same β-lactam antibiotic was used in both study arms (relative risk 1.12; 95% CI 0.96–1.29, Table 1), but hetereogeneity was noted between this subset of clinical studies ($P = 0.056$). In contrast, studies comparing different β-lactams provided pooled relative-risk results favouring monotherapy (relative risk 0.86; 95% CI 0.80–0.93, Table 1) without heterogeneity. The same result was observed in the subgroups of patients with microbiologically defined infections and those with haematological malignancies. Infection related mortality was reported in 25 trials, including 5074 patients. Overall results significantly favoured monotherapy (relative risk 0.76; 95% CI 0.59–0.98, $P = 0.03$), with a similar relative risk for studies comparing the same β-lactam and studies comparing different β-lactams (Table 1).

The rate of bacterial superinfections was similar in both groups. Fungal superinfections were more common in the combination treatment group, but the difference did not reach statistical significance. Adverse events occurred significantly less frequently in the monotherapy arm than in the combination treatment arm, especially nephrotoxicity (relative risk 0.42; 95% CI 0.32–0.56), even in the four studies in which once-daily dosing had been used (relative risk 0.20; 95% CI 0.04–0.90). Severe nephrotoxicity, as defined in the studies, was also significantly higher for patients treated with β-lactam–aminoglycoside combination therapy.

4.3. *Meta-analysis 2*

The second meta-analysis by Furno et al. was based on 29 randomised controlled trials comparing monotherapy to combination treatment with an aminoglycoside. A total number of 4795 febrile episodes were analysed of which 1029 were associated with bacteraemia.[11] The primary outcome measure was treatment failure defined as an inadequate clinical response, requiring modification of antibiotic therapy, or resulting in death. In 20 studies, the odds ratios favoured monotherapy and in 8 combination therapy. The pooled odds ratio for clinical failure with monotherapy versus combination therapy was 0.88 (95% CI 0.78–0.99), thus favouring monotherapy (Table 1). However, analysis of higher quality studies and subgroup analyses of patients with severe neutropaenia did not show any significant difference between monotherapy and combination treatment. Analyses of patients more than 14-year-olds and evaluation of bacteraemic episodes showed marginally significant differences favouring monotherapy.

4.4. *Additional studies*

Results of the nine trials that were not included in previous meta-analyses are summarised in Table 2. All-cause mortality was assessed in three trials; their combined results were similar to those obtained in the previous meta-analysis (relative risk 0.80; 95% CI 0.38–1.67). Treatment failure, defined most commonly as lack of defervescence within 72 h or need for antibiotic modification, was assessed in all trials; no significant difference between monotherapy and combination therapy was found in all but one trial comparing piperacillin-tazobactam to ceftriaxone,[18] where monotherapy was advantageous. Other outcomes are detailed in Table 2. Overall, the results were similar to those observed in the previous meta-analyses.

In summary, the review of the literature shows that monotherapy with a broad-spectrum β-lactam

Table 2 – Summary of the main results of randomised controlled trials not included in previous meta-analyses

Study	No. of episodes	Treatment	Patients with AL (%)	All-cause mortality (n/N)	Infection-related mortality (n/N)	Treatment failure (%)	Failure with bacteraemia (n/N)	Super-infections (%)
Bilgir et al. [16]	40	Imipenem versus Piperacillin/ tazobactam + amikacin	Haematological malignancies	NR	NR	M: 35; C: 40	NR	NR
Bru et al. [15]	M: 46 C: 54	Ticarcillin/clavulanate versus Ticarcillin/clavulanate + amikacin	Allogeneic stem cell Tx	NR	NR	M: 17.1; C: 15.5	M: 4/15; C: 1/13	M: 6.5; C: 13
Gaytan-Martinez et al. [17]	M: 63; C: 54	Cefepime versus ceftazidime + amikacin	AL+NHL	NR	NR	M: 14.2; C: 12.9	NR	NR
Gorschluter et al. [18]	M: 98; C: 85	Piperacillin/tazobactam versus Ceftriaxone + gentamicin	M: 85.7; C: 82.4	M: 5/98; C: 8/85	M: 4/98; C: 6/85	M: 42.9; C: 64.7[a]	M: 14/24; C: 19/25	NR
Kiel et al. [14]	M: 35; C: 35	Piperacillin/tazobactam versus Piperacillin/tazobactam + netilmicin	All	NR	NR	M: 40; C: 33	NR	NR
Kliasova et al. [13]	M: 23 C: 20	Meropenem versus Ceftazidime + amikacin	Bone marrow Tx	M: 1/22; C: 2/20	NR	M: 35; C: 50	NR	NR
Miller et al. [19]	M: 45; C: 41	Imipenem versus Piperacillin + tobramicin	NR	NR	NR	M: 10; C: 24	NR	M: 18; C: 7
Tamura et al. [20]	M: 95; C: 94	Cefepime versus Cefepime + amikacin	M: 47.4; C: 47.9	M: 7/95; C: 5/94	NR	M: 67.4; C: 56.3	M: 3/4; C: 4/7	NR
Wrzesien-Kus et al. [12]	M: 19 C: 21	Cefepime versus Cefepime + amikacin	NR	NR	NR	M: 52.6; C: 47.6	NR	NR

M: monotherapy; C: combination therapy; NR: not reported; AL: acute leukaemia; NHL: non-Hodgkin's lymphoma; Tx: transplantation.
a Significant advantage to monotherapy, $P = 0.0047$; no significant difference between monotherapy and combination therapy for all other comparisons.

antibiotic is as efficacious as and less toxic (especially nephrotoxic) than combination therapy with a β-lactam and an aminoglycoside.

4.5. *Once daily versus multiple daily dosing of aminoglycosides*

Eight randomised controlled trials compared the efficacy and safety of once versus thrice daily aminoglycoside therapy in febrile neutropaenic patients.[37–44] Four of these trials have been evaluated in a previous meta-analysis.[45] Clinical failure and mortality rates were similar in patients treated with once daily or thrice daily aminoglycosides (risk ratio 0.97; 95% CI 0.91–1.05 for clinical failure and 0.93; 95% CI 0.62–1.41 for mortality). The pooled nephrotoxicity risk ratio was somewhat lower in once-daily regimens than in multiple daily regimens (0.78; 95% CI 0.31–1.94), but did not reach statistical significance. Two additional studies compared single daily amikacin with ceftriaxone versus thrice daily amikacin with ceftazidime and showed similar efficacy and toxicity rates.[38,39] Sung et al. compared once versus thrice daily tobramycin combined with either piperacillin or ceftazidime. A statistically significant higher efficacy and a trend towards lower nephrotoxicity were noted in the once-daily regimen.[37] Torfoss et al. compared tobramycin given once versus three times a day in combination with penicillin for febrile patients with acute leukaemia or lymphoma and severe neutropaenia.[43] Efficacy and toxicity rates were similar in the aminoglycoside treatment groups.

In summary, the evidence gathered in several randomised controlled trials indicates that once daily dosing of an aminoglycoside is as efficacious as and probably less nephrotoxic than multiple daily dosing among neutropaenic patients. Similar results have been obtained in multiple randomised trials and several meta-analyses conducted in non-neutropaenic patients.[46–52]

4.6. *Recommendations for aminoglycosides in international guidelines*

Recent guidelines on the use of antimicrobial agents for the management of febrile neutropaenia have also addressed the issue of the use of aminoglycosides. In the guidelines of the Infectious Diseases Society of America (2002), β-lactam monotherapy (cefepime, ceftazidime, imipenem, meropenem and possibly piperacillin-tazobactam) was considered equivalent to combination therapy for empirical therapy of uncomplicated episodes of febrile neutropaenia.[9] In the case of progression of infection or development of a complication, the guidelines suggested that consideration be given to addition of an appropriate antibiotic or a change to different antibiotics. There was no specific recommendation regarding aminoglycoside-dosing schedule.

The guidelines of the Infectious Diseases Working Party of the German Society of Haematology and Oncology (2003) listed monotherapy (ceftazidime, cefepime, imipenem/cilastatin, meropenem and piperacillin-tazobactam) and combination therapy (acylaminopenicillin or third- or fourth-generation cephalosporins plus an aminoglycoside) as equivalent options for first-line treatment.[53] In case of persistence of fever and neutropaenia 6–9 days after initial antibiotic therapy, once or thrice-daily administration of amikacin and netilmicin was recommended as a treatment option in patients at intermediate risk who had been initially treated with monotherapy.

In the guidelines of the National Comprehensive Cancer Network (2005), broad-spectrum monotherapy was considered comparable to β-lactam aminoglycoside combination therapy. However, treatment with an anti-pseudomonal β-lactam with an aminoglycoside was recommended as first line therapy in clinically unstable patients (e.g. hypotension) or in patients at high-risk for *P. aeruginosa* infection.[54] The guidelines also recommend that the addition of an aminoglycoside to the initial antibiotic regimen be considered for patients with persistent fever, those who are clinically unstable and for microbiologically defined *P. aeruginosa* infections. There was no recommendation for the use of once-daily dosing of aminoglycosides.

5. Recommendations

The recommendations are summarised in Table 3 and are detailed below.

(1) Is β-lactam monotherapy as efficacious as a combination of a β-lactam plus an aminoglycoside for upfront empirical therapy in high-risk febrile neutropaenic patients with acute leukaemia or HSCT?

Answer: Yes, grading AI.

Comments: Available evidence shows that monotherapy is at least as efficacious as β-lactam-aminoglycoside combination therapy with regard to overall survival, overall response defined as a resolution of fever or of infection without modification of the initial antibiotic regimen, response of documented Gram-negative infections, and infection-related mortality. The monotherapies evaluated in these trials included ceftazidime, cefepime, imipenem/cilastatin, meropenem and piperacillin/tazobactam. Local advantages and disadvantages to each of the monotherapies may influence selection of the specific monotherapy. Ceftazidime may be inadequate in settings with high prevalence of extended spectrum β-lactamases producing microorganisms and is less active against Gram-positive bacteria;[55] imipenem has been associated with increased rates of pseudomembranous colitis;[56,57] piperacillin-tazobactam is associated with false-positive galactomannan assays;[58] and cefepime was associated with higher all-cause mortality when compared to other monotherapies in randomised trials.[56] Thus, the appropriate β-lactam for monotherapy should be selected according to local epidemiology, antibiotic resistance patterns, recent β-lactam use and available evidence.

(2) Is a combination of a β-lactam plus an aminoglycoside more nephrotoxic or ototoxic than β-lactam monotherapy?

Answer: Yes, grading AI for both nephrotoxicity and ototoxicity.

Table 3 – Summary of recommendations

Problem	Recommendation	Grading[a]
BL monotherapy is as efficacious as BL + AG as empirical therapy of febrile neutropaenia	Yes	A I
BL + AG combination is more nephrotoxic and ototoxic than BL monotherapy	Yes	A I
OD dosing of AG are as efficacious as and less nephrotoxic than MDD	Yes	A I
Empirical addition of AG to the initial regimen in patients with persistent fever	No	C III
Empirical use of BL + AG combination in patients in whom a resistant Gram-negative infection[b] is suspected	Yes	C III
Addition of AG to the initial regimen in case of documented *P. aeruginosa* infection	No	C III
Use of BL + AG combination in patients with severe sepsis or septic shock	Yes	C III
Use of BL + AG in neutropaenic patients with pneumonia	No	C III
Use of BL + AG combination to prevent emergence of resistance during therapy	No	B I

BL: β-lactam; AG: aminoglycoside; OD: once-daily dosing; MDD: multiple-daily dosing.
a Level of evidence and level of recommendation.[9]
b Local epidemiology and previous antibiotic treatments should be taken into account.

Comments: Nephrotoxicity was evaluated in several trials comparing monotherapy with combination therapy. Amikacin, netilmicin, gentamicin and tobramycin were the aminoglycosides used in these trials. Nephrotoxicity and severe nephrotoxicity occurred significantly more often among patients treated with combination therapy than in those treated with monotherapy. The number needed to prevent one episode of nephrotoxicity when using β-lactam monotherapy was 31.[10] Among 14 trials reporting ototoxicity, 19 patients developed ototoxicity in the combination treatment arm versus three patients in the monotherapy arm (unpublished data from Paul et al.[10]). Routine monitoring for ototoxicity with audiometry was rarely performed in these studies.

(3) Is there evidence that once-daily administration of aminoglycosides is as efficacious as and potentially less toxic than multiple-dose administration for febrile neutropaenic patients?

Answer: Yes, grading AI.

Comments: Results from several randomised controlled trials suggest that survival rates and efficacy (as assessed by successful treatment without the need for modification of antibiotic therapy) are similar for high-risk neutropaenic patients treated with either once daily or multiple dose administration of aminoglycosides. Moreover, nephrotoxicity was less frequent among patients treated with once-daily dosing.

(4) Is there evidence supporting the empirical addition of an aminoglycoside to patients initially treated with monotherapy with persistent fever?

Answer: No, grading CIII.

Comments: We are not aware of clinical trials that have addressed that question for patients with persistent fever.

(5) Are there specific clinical conditions justifying the use of an aminoglycoside as part of the empirical antibiotic regimen? Specific clinical conditions for which the use of an aminoglycoside might be considered include a high suspicion or microbiological documentation of an infection caused by *P. aeruginosa* or resistant Gram-negative bacilli, pneumonia and the occurrence of life-threatening conditions, such as severe sepsis or septic shock. We will consider each of these possible indications below.

(a) Suspicion of infections caused by resistant *P. aeruginosa* or other resistant Gram-negative bacteria.

Answer: Yes, grading CIII.

Comments: There are no data to support the empirical use of a combination of an aminoglycoside and a β-lactam antibiotic for treating infections suspected to be due to resistant Gram-negative bacilli (including *P. aeruginosa*). However, given the risk of poor outcome in neutropaenic patients treated with inappropriate antibiotics, especially in centres where resistant Gram-negative bacteria are a concern, we recommend using a combination therapy as empirical regimen until microbiological data become available. The aminoglycoside should be discontinued as soon as resistance to the β-lactam antibiotic has been ruled out.

(b) Documented *Pseudomonas aeruginosa* infections

Answer: No, grading CIII.

Comments: In the meta-analysis by Paul et al. no significant differences were observed between monotherapy and combination therapy with respect to the subgroup of patients with documented *P. aeruginosa* infections.[10] Only 58 patients were assessed for mortality and 139 patients for treatment failure. In a meta-analysis including non-neutropaenic patients, a significant survival benefit for combination therapy was found in the subgroup of patients with *P. aeruginosa* bacteraemia.[59] However, this meta-analysis included observational studies, a heterogenous patient population and single aminoglycoside treatment in the monotherapy arm, precluding firm conclusion regarding β-lactam monotherapy. Thus, there is no proven advantage of adding an

aminoglycoside to a β-lactam antibiotic when the *P. aeruginosa* is fully susceptible to the β-lactam agent. In fact, susceptibility of gram-negative bacilli to the β-lactam used is a primary determinant of outcome.[60]

(c) Severe sepsis and septic shock.

Answer: Yes, grading CIII.

Comments: Severe sepsis and septic shock occur in only 1–2% of febrile neutropaenic episodes.[61,62] However, given that patients with septic shock often are excluded from many clinical studies, the incidence of these complications might be underestimated. In a logistic regression analysis of patient's outcome performed in 909 neutropaenic cancer patients with bacteraemia, the risk of death was significantly increased in hypotensive patients.[63] Although no data are available, it is recommended to use an aminoglycoside antibiotic in febrile neutropaenic patients with severe sepsis or septic shock.

(d) Pneumonia.

Answer: No, grading CIII.

(6) Does the use of β-lactam-aminoglycoside combinations in neutropaenic patients prevent the emergence of resistant bacteria?

Answer: No, grading BI.

Comments: Current evidence indicates that β-lactam monotherapy is not associated with an increased risk of emergence of resistant bacteria when compared with β-lactam and aminoglycoside combinations. Paul et al. assessed bacterial superinfections as a surrogate marker of induction of resistance. No difference was found between combination and monotherapy.[10] Only two studies compared the frequency of colonisation with resistant Gram-negative bacteria after treatment, which occurred in 5 of 152 patients (3%) treated with monotherapy and in 1 of 152 patients (0.6%) treated with a combination of antibiotics.[64,65] Bliziotis et al. conducted a meta-analysis of randomised controlled trials aimed at comparing the effect of combinations of an aminoglycoside and a β-lactam antibiotic and of β-lactam monotherapy on the emergence of antimicrobial resistance among non-neutropaenic patients.[66] Beta-lactam monotherapy was associated with fewer superinfections, while treatment failure attributable to resistance induction or superinfections did not differ significantly between the two study arms. Thus, data from randomised trials do not suggest that the use of an aminoglycoside-containing antibiotic regimen is associated with a reduced risk of the emergence of resistant bacteria.

Conflict of interest statement

The authors L.D., M.P., F.M. and G.B. declares no conflict of interest. T.C. has received grants and research supports from Bayer, Bristol-Myers Squibb, Merck Sharp & Dohme-Chibret, Wyeth and Astra-Zeneca, and has been a consultant for Merck Sharp & Dohme-Chibret.

Sources of support

The ECIL 1 meeting has been supported by unrestricted educational grants from Astellas Pharma, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp Dohme, Schering Plough, Wyeth and Zeneus Pharma.

Acknowledgements

This manuscript was internally reviewed by R. de la Cámara, Servicio de Haematologia, Hospital de la Princessa, Madrid, Spain. J P. Donnelly, Department of Haematology, Radboud University Medical Centre and University Centre for Infectious Diseases, Nijmegen, The Netherlands. We thank them for their thorough review and insightful comments.

All the members of the Organising Committee and the Conference participants express their sincere thanks to the sponsors who supported the meeting and shared our enthusiasm for this first conference: Astellas Pharma, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp Dohme, Schering Plough, Wyeth and Zeneus Pharma. The ECIL 1 meeting has been organised by Société Kobe, Groupe GL Events, 10, quai Charles de Gaulle, Cité Internationale, 69463 Lyon Cedex 06, France.

REFERENCES

1. Schimpff S, Satterlee W, Young VM, et al. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med* 1971;**284**:1061–5.
2. Schimpff SC. Empiric antibiotic therapy for granulocytopenic cancer patients. *Am J Med* 1986;**80**:13–20.
3. Hughes WT, Armstrong D, Bodey GP, et al. From the Infectious Diseases Society of America. Guidelines for the use of antimicrobial agents in neutropaenic patients with unexplained fever. *J Infect Dis* 1990;**161**:381–96.
4. Hughes WT, Armstrong D, Bodey GP, et al. guidelines for the use of antimicrobial agents in neutropaenic patients with unexplained fever. Infectious Diseases Society of America. *Clin Infect Dis* 1997;**25**:551–73.
5. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropaenic cancer patients. *J Clin Oncol* 2000;**18**:3038–51.
6. Talcott JA, Siegel RD, Finberg R, et al. Risk assessment in cancer patients with fever and neutropaenia: a prospective, two-centre validation of a prediction rule. *J Clin Oncol* 1992;**10**:316–22.
7. Vidal L, Paul M, Ben dor I, et al. Oral versus intravenous antibiotic treatment for febrile neutropaenia in cancer patients: a systematic review and meta-analysis of randomized trials. *J Antimicrob Chemother* 2004;**54**:29–37.
8. Ramphal R. Changes in the etiology of bacteraemia in febrile neutropaenic patients and the susceptibilities of the currently isolated pathogens. *Clin Infect Dis* 2004;**9**(Suppl. 1):S25–31.
9. Hughes WT, Armstrong D, Bodey GP, et al. guidelines for the use of antimicrobial agents in neutropaenic patients with cancer. *Clin Infect Dis* 2002;**34**:730–51.
10. Paul M, Soares-Weiser K, Grozinsky S, et al. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in

cancer patients with neutropaenia. *Cochrane Database Syst Rev* 2003;**2**:CD003038.
11. Furno P, Bucaneve G, Del Favero A. Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropaenic patients: a meta-analysis. *Lancet Infect Dis* 2002;**2**:231–42.
12. Wrzesien-Kus AJ, Wierzbowska K, Robak AT. Cefepine in monotherapy or in combination with amikacine as the empirical treatment of febrile neutropaenic patients. *Acta Haematol Pol* 2001;**32**:165–72.
13. Kliasova G, Savchenko VLL, Mendeleeva L, et al. (Moscow, RUS). Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for febrile neutropaenic bone marrow transplant patients. In: 11th European Congress of clinical microbiology and infectious diseases; 2001.
14. Kiehl MG, Bischoff M, Basara N, et al. A prospective randomized trial comparing the efficacy and safety of piperacillin/tazobactam versus piperacillin/tazobactam plus netilmicin in the treatment of febrile neutropenia in allogeneic stem cell recipients. In: *41st interscience conference on antimicrobial agents and chemotherapy*, Chicago. Americal Society for Microbiology; 2001.. p. 267.
15. Bru JP, Michallet M, Legrand C, et al. A prospective randomized study comparing the efficacy of Timentin alone or in combination with amikacin in the treatment of febrile neutropaenic patients. *J Antimicrob Chemother* 1986; **17**(Suppl. C):203–9.
16. Bilgir O, Kadikoylu V, Bilgir F. The comparison of imipenem with piperacillin/tazobactam and amikacin combination in patients with haematological malignancies in the treatment of febrile neutropaenia. In: 10th Congress of the European haematology association, Stockholm, Sweden; 2005 [abstract no. 1021].
17. Gaytan-Martinez JE, Mateos-Garcia E, Casanova LJ, et al. Efficacy of empirical therapy with cefepime compared with ceftazidime plus amikacin in febrile neutropaenic patients. In: Annual meeting of the American society of haematology; 2002 [abstract no. 3655].
18. Gorschluter M, Hahn C, Fixson A, et al. Piperacillin-tazobactam is more effective than ceftriaxone plus gentamicin in febrile neutropaenic patients with haematological malignancies: a randomized comparison. *Support Care Cancer* 2003;**11**:362–70.
19. Miller JA, Butler T, Beveridge RA, et al. Efficacy and tolerability of imipenem-cilastatin versus ceftazidime plus tobramycin as empiric therapy of presumed bacterial infection in neutropaenic cancer patients. *Clin Ther* 1993;**15**:486–99.
20. Tamura K, Imajo K, Akiyama N, et al. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropaenia. *Clin Infect Dis* 2004;**39**(Suppl. 1):S15–24.
21. Antmen B, Sasmaz I, Tanyeli A et al. Initial empiric antibiotic treatments in childhood febrile neutropaenia: meropenem versus ceftazidime plus amikacin combination. In: 11th European congress of clinical microbiology and infectious diseases; 2001.
22. Corapcioglu F, Sarper N. Cefepime versus ceftazidime + amikacin as empirical therapy for febrile neutropaenia in children with cancer: a prospective randomized trial of the treatment efficacy and cost. *Pediatr Haematol Oncol* 2005;**22**:59–70.
23. El Haddad A. Comparison of cefoperazone-sulbactam versus piperacillin plus amikacin as empiric therapy in pediatric febrile neutropaenic cancer patients. *Curr Therapeut Res Clin Exp* 1995;**56**:1094–9.
24. Hung KC, Chiu HH, Tseng YC, et al. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empirical therapy for neutropaenic fever in children with malignancy. *J Microbiol Immunol Infect* 2003;**36**:254–9.
25. Koehler M, Bubala H, Sonta-Jakimczyk D, et al. Assessment of the efficacy of treating infections in haematopoietic proliferative diseases: Monotherapy with ceftazidime and tobramycin combined with amoxycillin/ampicillin [in Polish]. *Pol Tyg Lek* 1990;**45**:417–20.
26. Petrilli AS, Cypriano M, Dantas LS, et al. Evaluation of ticarcillin/clavulanic acid versus ceftriaxone plus amikacin for fever and neutropaenia in pediatric patients with leukaemia and lymphoma. *Braz J Infect Dis* 2003;**7**: 111–20.
27. Ahmed-El Borollosy N, El Beshlawy A, El Mahallawy H, et al. Outpatient single dose ceftriaxone and amikacin versus imipenem/cilastatin monotherapy in the empiric treatment of pediatric patients with high risk fever and neutropenia. A randomized, prospective clinical trial. In: American society of haematology annual meeting abstracts; 2003.
28. Ahmed-El Borollosy N, El Beshlawy A, El Mahallawy H, et al. Outpatient single dose ceftriaxone and amikacin versus imipenem/cilastatin monotherapy in the empiric treatment of pediatric patients with high risk fever aneutropaenia. A randomized, prospective clinical trial. In: American society of clinical oncology conference; 2004.
29. Jimeno A, Arcediano A, Gomez C et al. Randomized study of cefepime versus ceftazidime plus amikacin in febrile neutropaenic patients with solid tumors treated with high dose chemotherapy and peripheral blood stem cell support. In: Proceedings of the American society of clinical oncology; 2003 [abstract no. 3387].
30. Rodriguez W, Gomez H, Silva ME, et al. Cefotaxima versus cefalotina-gentamicina en el primer episodio febril de pacientes con tumores solidos y neutropaenia de corta duracion / Cefotaxime vs Cephalotin-Gentamicin in the first febrile episode of patients having solid tumors and short-term neutropaenia. *Acta Cancerol* 1995;**25**:61–8.
31. Berezin EN, Almeida FJ, Santos AG et al. Asessment of Cefepime monotherapy versus combined therapy with ceftriaxone and aminoglicosyde in oncologic children and adolescents with febrile neutropaenia. In: 13th European congress of clinical microbiology and infectious diseases; 2003.
32. Sanz MA, Bermudez A, Rovira M, et al. Imipenem/cilastatin versus piperacillin/tazobactam plus amikacin for empirical therapy in febrile neutropaenic patients: results of the COSTINE study. *Curr Med Res Opin* 2005;**21**:645–55.
33. Caldas J, Fernandes T, Monteiro A et al. Management of febrile neutropaenia: single agent or combination therapy. In: American society of haematology annual meeting abstracts; 2004 [abstract no. 5063].
34. Badea M, Badea D. Ceftriaxone in febrile granulocytopenic patients with haematological malignancies. In: European haematology association conference; 2002 [abstract no. 707].
35. Akin H, Korten V, Akan H et al. Cefepime combined with a short (four days) or long course of isepamicin for empirical therapy of high-risk febrile neutropaenic haematological cancer patients: a prospective, randomised, multicentre study. In: European congress of clinical microbiology and infectious diseases; 2005 [abstract no. R2061].
36. Fainstein V, Bodey GP, Elting L, et al. A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infections in cancer patients. *J Antimicrob Chemother* 1983;**12**(Suppl. A):101–10.
37. Sung L, Dupuis LL, Bliss B, et al. Randomized controlled trial of once- versus thrice-daily tobramycin in febrile neutropaenic children undergoing stem cell transplantation. *J Natl Cancer Inst* 2003;**95**:1869–77.

38. Ariffin H, Arasu A, Mahfuzah M, et al. Single-daily ceftriaxone plus amikacin versus thrice-daily ceftazidime plus amikacin as empirical treatment of febrile neutropaenia in children with cancer. *J Paediatr Child Health* 2001;**37**:38–43.
39. Charnas R, Luthi AR, Ruch W. Once daily ceftriaxone plus amikacin versus three times daily ceftazidime plus amikacin for treatment of febrile neutropaenic children with cancer. Writing Committee for the International Collaboration on Antimicrobial Treatment of Febrile Neutropenia in Children. *Pediatr Infect Dis J* 1997;**16**:346–53.
40. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. *Ann Intern Med* 1993;**119**:584–93.
41. Rozdzinski E, Kern WV, Reichle A, et al. Once-daily versus thrice-daily dosing of netilmicin in combination with beta-lactam antibiotics as empirical therapy for febrile neutropaenic patients. *J Antimicrob Chemother* 1993;**31**: 585–98.
42. Gibson J, Johnson L, Snowdon L, et al. Single daily ceftriaxone and tobramycin in the empirical management of febrile neutropaenic patients: a randomised trial. *Int J Haematol* 1993;**58**:63–72.
43. Torfoss D, Hoiby EA. Tobramycin once versus three times a day given with penicillin G to cancer patients with febrile neutropaenia: a prospective randomised multicentre trial. In: *16th European congress of clinical microbiology and infectious diseases*, Nice, France. European Society of Clinical Microbiology and Infectious Diseases; 2006. p. 698.
44. Hansen MA, Carstensen F, Coolidge C, Dahlager J, Frimodt-Moller J. Once versus thrice-daily dosing of netilmicin in febrile immunocompromised patients: a randomized, controlled study of efficacy and safety. *Journal of Drug Development* 1988;**1**(Suppl. 3):119–24.
45. Hatala R, Dinh TT, Cook DJ. Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review. *Clin Infect Dis* 1997;**24**:810–5.
46. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997;**24**:796–809.
47. Bailey TC, Little JR, Littenberg B, et al. A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997;**24**:786–95.
48. Barza M, Ioannidis JP, Cappelleri JC, et al. Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996;**312**:338–45.
49. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med* 1996;**124**:717–25.
50. Ferriols-Lisart R, Alos-Alminana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health Syst Pharm* 1996;**53**:1141–50.
51. Galloe AM, Graudal N, Christensen HR, et al. Aminoglycosides: single or multiple daily dosing? A meta-analysis on efficacy and safety. *Eur J Clin Pharmacol* 1995;**48**:39–43.
52. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother* 1996;**37**:645–63.
53. Link H, Bohme A, Cornely OA, et al. Antimicrobial therapy of unexplained fever in neutropaenic patients–guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). *Ann Haematol* 2003;**82**(Suppl. 2): S105–17.
54. NCCN. National Comprehensive Cancer Network. Clinical practice guidelines in oncology – fever and neutropenia. Available from: http://www.nccn.org/.
55. Rolston KV, Bodey GP. Comment on: Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2006;**58**:478.
56. Paul M, Yahav D, Fraser A, et al. Empirical antibiotic monotherapy for febrile neutropaenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2006;**57**:176–89.
57. Edwards SJ, Emmas CE, Campbell HE. Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. *Curr Med Res Opin* 2005;**21**:785–94.
58. Viscoli C, Machetti M, Cappellano P, et al. False-positive galactomannan platelia Aspergillus test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis* 2004;**38**:913–6.
59. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* 2004;**4**:519–27.
60. Klastersky J, Zinner SH, Calandra T, et al. Empiric antimicrobial therapy for febrile granulocytopenic cancer patients: lessons from four EORTC trials. *Eur J Cancer Clin Oncol* 1988;**24**(Suppl. 1):S35–45.
61. Cometta A, Zinner S, de Bock R, et al. Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *Antimicrob Agents Chemother* 1995;**39**:445–52.
62. Del Favero A, Menichetti F, Martino P, et al. A multicentre, double-blind, placebo-controlled trial comparing piperacillin-tazobactam with and without amikacin as empiric therapy for febrile neutropaenia. *Clin Infect Dis* 2001;**33**:1295–301.
63. Elting LS, Rubenstein EB, Rolston KV, et al. Outcomes of bacteraemia in patients with cancer and neutropaenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997;**25**:247–59.
64. Cornelissen JJ, de Graeff A, Verdonck LF, et al. Imipenem versus gentamicin combined with either cefuroxime or cephalothin as initial therapy for febrile neutropaenic patients. *Antimicrob Agents Chemother* 1992;**36**:801–7.
65. Norrby SR, Vandercam B, Louie T, et al. Imipenem/cilastatin versus amikacin plus piperacillin in the treatment of infections in neutropaenic patients: a prospective, randomized multi-clinic study. *Scand J Infect Dis* 1987;**52**(Suppl.):65–78.
66. Bliziotis IA, Samonis G, Vardakas KZ, et al. Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. *Clin Infect Dis* 2005;**41**:149–58.