Review: β-lactam alone was better than β-lactam plus aminoglycoside for cancer patients with neutropenia

Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. **Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia.** Cochrane Database Syst Rev. 2002(2):CD003038 (latest version 6 Jan 2002).

QUESTION

In febrile neutropenic patients with cancer, is β-lactam alone more effective than combination therapy with β-lactam plus aminoglycoside?

DATA SOURCES

Studies were identified by searching MEDLINE (to August 2001), EMBASE/Excerpta Medica (to 2000), the Cochrane Library (2001), LILACS (to October 2001), conference proceedings of the Interscience Conference of Antimicrobial Agents and Chemotherapy (1995 to 2001), and bibliographies of relevant studies and by contacting authors.

STUDY SELECTION

Studies were selected if they were randomized controlled trials (RCTs) that compared intravenous β-lactam with intravenous β-lactam plus aminoglycoside in febrile patients who had cancer and neutropenia induced by chemotherapy or bone-marrow transplantation. Studies of neonates and preterm babies were excluded.

DATA EXTRACTION

2 reviewers independently assessed the quality of study methods and extracted data on patients, interventions, and outcomes (including death, treatment failure, superinfection, and adverse events).

MAIN RESULTS

46 RCTs (7642 patients) were included (median sample size 94 patients). 5 RCTs included children only; 11 RCTs included both children and adults. Monotherapy and combination therapy did not differ for all-cause mortality or bacterial or fungal superinfections (Table). Monotherapy led to fewer treatment failures than combination therapy (Table), but statistically significant heterogeneity existed among these trials. No heterogeneity existed among RCTs comparing different β-lactams; fewer treatment failures occurred in the monotherapy group than in the combination-therapy group. When RCTs comparing the same β-lactams in both study arms were pooled, the treatment groups did not differ for treatment failure; statistically significant heterogeneity existed among these studies. Combination therapy led to more adverse events, particularly nephrotoxicity, than monotherapy (Table).

CONCLUSIONS

In febrile patients with cancer and neutropenia, β-lactam alone and β-lactam plus aminoglycoside do not differ for all-cause mortality or bacterial or fungal superinfections. Monotherapy decreases treatment failure and leads to fewer adverse events, particularly nephrotoxicity, than combination therapy.

Source of funding: European Union.

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β-lactam alone (monotherapy) vs β-lactam plus aminoglycoside (combination therapy) for cancer with fever and neutropenia*

Outcomes	Number of studies	Weighted event rates		RRR (95% CI)	NNT (CI)
		Monotherapy	Combination therapy		
All-cause mortality	29	8.7%	9.3%	15% (–2 to 28)	Not significant
Treatment failure	46	39%	42%	9% (1 to 15)	31 (16 to 334)†
Bacterial superinfection	24	11%	11%	3% (–14 to 18)	Not significant
Fungal superinfection	18	3.3%	3.9%	25% (–9 to 49)	Not significant
Any adverse event	35	23%	26%	17% (3 to 28)	40 (19 to 334)
Any nephrotoxicity	27	2.9%	5.5%	51% (35 to 64)	39 (24 to 100)
Severe nephrotoxicity	14	0.5%	0.9%	82% (37 to 95)	250 (125 to ∞)

*Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from data in article using a random-effects model. Length of follow-up not reported.

†Heterogeneity existed among studies.

COMMENTARY

Neutropenia occurs in cancer patients treated with cytoreductive chemotherapy, which renders them highly susceptible to bacterial infection. Empirical antibiotic treatment in this population reduces morbidity and mortality (1).

The rationale for empiric regimens with broad-spectrum penicillins or cephalosporins combined with an aminoglycoside was based on the synergistic activity of these antibiotics against gram-negative bacteria, including *Pseudomonas aeruginosa* (2). Other treatments have included double β-lactam combinations or a single drug (monotherapy) to avoid the toxicity associated with aminoglycosides. Recognition in the 1990s of the importance of gram-positive bacteria in causing infection in patients with febrile neutropenia led to the increased use of broad-spectrum cephalosporin and carbapenem monotherapy with greater gram-positive coverage (3).

Paul and colleagues have attempted to compare the effectiveness of β-lactam alone with β-lactam plus aminoglycoside in a meta-analysis. The study selection, outcomes, and data synthesis are all appropriate. Although statistically significant heterogeneity hampered the analysis of failure, no heterogeneity was encountered when the same β-lactam was used in both the monotherapy and combination arms. The combination was no more effective than the same β-lactam alone.

The results of this meta-analysis substantiate the current move away from β-lactam–aminoglycoside combination therapy. Monotherapy is conclusively more effective and less toxic.

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References

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2. **Klastersky J, Zinner SH.** Rev Infect Dis. 1982;4:294-301.
3. **Bochud PY, Calandra T, Francioli P.** Am J Med. 1994;97:256-94.

