Review: Additional anti–gram-positive antibiotics do not reduce all-cause mortality in cancer and febrile neutropenia

Paul M, Borok S, Fraser A, et al. **Additional anti-Gram-positive antibiotic treatment for febrile neutropenic cancer patients.** Cochrane Database Syst Rev. 2005;(3):CD003914.

Clinical impact ratings: Hospitalists ★★★★★☆☆ Infectious Disease ★★★★☆☆☆ Oncology ★★★★★★★

QUESTION

Does the addition of an anti–gram-positive (anti-GP) antibiotic to empirical therapy reduce all-cause mortality in patients with cancer and febrile neutropenia?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, LILACS, and Cochrane Central Register of Controlled Trials (all up to June 2004); conference proceedings; reference lists of relevant studies and reviews; and researchers in the field.

Study selection and assessment: Randomized or quasi-randomized controlled trials (RCTs) comparing a standard antibiotic regimen with the same regimen plus an anti-GP antibiotic for empirical treatment of patients with cancer and febrile neutropenia. Quality assessment of individual studies was based on allocation sequence, allocation concealment, blinding, intention-to-treat analysis, and dropout rate.

Outcomes: All-cause mortality, treatment failure, and GP superinfection.

MAIN RESULTS

13 RCTs (n = 2392, age range 1 to 88 y) met the selection criteria. Meta-analysis of 7 RCTs (n = 852) showed that the addition of an anti-GP antibiotic did not reduce all-cause mortality (Table). The addition of an anti-GP antibiotic resulted in fewer treatment failures if treatment modifications were counted as failures, but not if treatment modifications were ignored (Table). Fewer GP superinfections occurred in the additional anti-GP antibiotic group (Table), but no data were available about colonization with resistant bacteria.

CONCLUSION

The addition of anti–gram-positive antibiotics to standard empirical therapy does not reduce all-cause mortality in patients with cancer and febrile neutropenia.

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Addition of an anti–gram-positive (anti-GP) antibiotic to standard empirical antibiotics vs standard empirical antibiotics for cancer and febrile neutropenia*

Outcomes at 30 days	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Empirical with anti-GP	Empirical without anti-GP		
Overall mortality	7 (852)	10%	12%	18% (–20 to 44)	Not significant
Treatment failure (treatment modifications counted)	10 (1779)	33%	44%	24% (15 to 32)	10 (7 to 14)
Overall treatment failure (treatment modifications ignored)	6 (943)	19%	19%	0% (–27 to 21)	Not significant
GP superinfections	9 (1688)	2.1%	8.1%	76% (60 to 86)	17 (13 to 25)

*Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from data in article using a fixed-effects model.

COMMENTARY

Most GP cocci that cause bacteremia in neutropenic patients are resistant to the β-lactam antibiotics used empirically, so the question of using an additional anti-GP antibiotic up front, especially a glycopeptide, is important. To better understand the stakes, one must first appreciate that the GP bacteria faced in this situation fall into 2 categories. The first category includes coagulase-negative staphylococci, *Corynebacterium jeikeium*, stomatococci, and enterococci, which are usually indolent, so treatment can often be safely deferred until formal microbiological identification (1). The second category includes *Streptococcus viridans* and *Staphylococcus aureus*, which are virulent, are often resistant to penicillin and methicillin, and can cause substantial morbidity and mortality before formal microbiological identification (2).

Paul and colleagues analyzed data from 13 RCTs to determine whether adding anti-GP antibiotics reduced mortality and morbidity in patients with cancer and febrile neutropenia after chemotherapy.

Their review consolidates the findings of the individual trials, namely that adding anti-GP antibiotics does not improve survival or success rates. The proportions of methicillin-resistant *S. aureus* and penicillin-resistant *S. viridans* were not reported.

Does adding an anti-GP antibiotic cause further harm? No increases were seen in fungal superinfections or nephrotoxicity, but skin reactions were more common in the review. A major limitation of the studies in this review is the lack of information about the emergence of resistant bacteria.

The addition of an anti-GP antibiotic should not be part of the initial empirical treatment of febrile neutropenia in patients with cancer.

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2. **Bochud PY, Calandra T, Francioli P.** Bacteremia due to viridans streptococci in neutropenic patients: a review. Am J Med. 1994;97:256-64.