THERAPEUTICS

Review: Antibiotic prophylaxis reduces mortality in patients with neutropenia after chemotherapy

Gafter-Gvili A, Fraser A, Paul M, et al. **Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy.** Cochrane Database Syst Rev. 2005;(4):CD004386.

Gafter-Gvili A, Fraser A, Paul M, Leibovici L. **Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients.** Ann Intern Med. 2005;142:979-95.

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

QUESTION

Does antibiotic prophylaxis, particularly with a fluoroquinolone, reduce mortality in afebrile patients with neutropenia after chemotherapy?

METHODS

Data sources: MEDLINE (1966 to 2004), EMBASE/Excerpta Medica (1980 to 2004), Cochrane Cancer Network register of trials (December 2004), Cochrane Library (Issue 4, 2004), meeting abstracts, references of included studies and reviews, and experts in the field.

Study selection and assessment: Published and unpublished randomized controlled trials (RCTs) or quasi-RCTs in any language that compared antibiotic therapy with placebo, no intervention, or other antibiotics for prophylaxis of bacterial infections in patients with afebrile neutropenia after chemotherapy for malignant disease. Quality assessment of individual studies was based on allocation concealment, generation of allocation sequence, blinding, and intention-to-treat analysis.

Outcomes: All-cause mortality. Secondary outcomes were infection-related mortality, fungal infection, adverse events, and the emergence of drug-resistant bacilli.

MAIN RESULTS

100 RCTs (n = 10 274, mostly adults) met the selection criteria. 66 trials included only patients with hematologic cancer, and 29 trials included patients with bone marrow transplants. Meta-analyses showed that antibiotic prophylaxis reduced all-cause mortality and infection-related mortality (Table) and did not increase fungal infections (relative risk increase [RRI] 7%, 95% CI −17 to 37), but did increase adverse events (RRI 58%, CI 34 to 86) more than placebo or no intervention. Trials of fluoroquinolone prophylaxis also showed reduced all-cause mortality and infection-related mortality (Table) and increased adverse events (RRI 59%, CI 9 to 83), but did not affect fungal infections (relative risk reduction 17%, CI −22 to 44) or the emergence of drug-resistant bacilli (RRI 69%, CI −27 to 292).

CONCLUSIONS

Antibiotic prophylaxis reduces all-cause and infection-related mortality in patients with afebrile neutropenia after chemotherapy, but increases adverse events.

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Antibiotic prophylaxis vs placebo or no intervention (control) for afebrile neutropenia*

Outcomes	Intervention	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
			Intervention	Control		
All-cause mortality	Antibiotics	41 (3585)	8.0%	12%	34% (21 to 46)	25 (17 to 50)
	Fluoroquinolone	15 (1919)	4.2%	8.2%	48% (26 to 63)	25 (17 to 50)
Infection-related mortality	Antibiotics	37 (2937)	5.4%	9.4%	42% (26 to 55)	25 (17 to 50)
	Fluoroquinolone	10 (1022)	1.9%	6.9%	62% (31 to 79)	20 (15 to 50)

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

COMMENTARY

Currently, the overall mortality for neutropenic cancer patients with documented bacteremia is about 7% (1). The use of empirical antibiotics for neutropenic patients who develop fever is standard, but the use of prophylactic antibiotics before fever occurs remains controversial and is not recommended in current guidelines (2). Recent studies of fluoroquinolone prophylaxis showed decreased rates of fever and infection (3, 4), but were not adequately powered for effects on mortality.

The review by Gafter-Gvili and colleagues showed a reduction in all-cause and infection-related mortality with antibiotic prophylaxis, particularly with a fluoroquinolone, compared with placebo or no intervention. This is the largest review to date (100 RCTs) on this topic.

Should antibiotic prophylaxis be routinely administered to such patients? Several areas warrant further discussion. The review suggested an increase in fluoroquinolone-resistant bacteria that did not reach statistical significance. Most of the included studies were not specifically designed to measure the emergence of resistance, so pooling their results does not provide a definitive answer. Other studies have shown an increase in fluoroquinolone-resistant bacilli with prophylaxis (5). All antibiotics come with a price tag. The absolute risk reductions found in this review are small: 4% for all-cause mortality and 4% for infection-related mortality.

We are left with many unanswered questions. The biggest are: What effect would a policy of broadly applied prophylaxis have on resistance in an individual cancer center and worldwide? Can we better identify patients who are at greatest risk for infection-related mortality where the benefits of prophylaxis clearly outweigh the risks? The current Infectious Diseases Society of America guideline: "An axiom for prophylaxis is that the antibiotic should be administered for as short a period as possible to as few patients as possible," seems appropriate until these questions are answered (2).

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