Review: Antifungal agents do not reduce mortality in neutropenia caused by chemotherapy or bone marrow transplantation

Gøtzsche PC, Johansen HK. **Routine versus selective antifungal administration for control of fungal infections in patients with cancer.** Cochrane Database Syst Rev. 2002;(2):CD000026 (latest version 9 Jan 2002).

QUESTION

In patients with cancer and neutropenia caused by chemotherapy or bone marrow transplantation (BMT), do antifungal agents reduce mortality?

DATA SOURCES

Studies were identified by searching 2 electronic databases, conference abstracts, and bibliographies and by contacting pharmaceutical manufacturers.

STUDY SELECTION

Studies were selected if they were randomized controlled trials (RCTs) comparing antifungal agents with placebo or no treatment in patients with cancer and neutropenia caused by chemotherapy or BMT.

DATA EXTRACTION

Data were extracted on patients, intervention, treatment duration, length of follow-up, randomization, blinding, and outcomes (deaths, invasive fungal infections [IFIs], colonization, and use of rescue drugs).

MAIN RESULTS

30 RCTs (4094 patients) were included. Patients had leukemia in 19 RCTs and BMT in 11 RCTs. Antifungal agents were given prophylactically in 27 RCTs and empirically in 3 RCTs. Treatment groups did not differ for mortality overall (Table) or when grouped by type of antifungal agent. Antifungal agents led to fewer infections overall; the treatment effect was seen for amphotericin, fluconazole, and itraconazole but not for ketoconazole or miconazole (Table).

Studies on colonization rates and use of rescue drugs were heterogeneous; antifungal agents led to lower rates of colonization and use of rescue drugs than did placebo or no treatment (Table).

CONCLUSIONS

In patients with cancer and neutropenia caused by chemotherapy or bone marrow transplantation, antifungal agents do not reduce mortality. Amphotericin, fluconazole, and itraconazole reduce invasive infection. Colonization and use of rescue drugs are reduced by antifungal agents.

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Antifungal agents vs placebo or no treatment for cancer with neutropenia*

Outcomes	Antifungal agent	Number of trials	Weighted event rates		RRR (95% CI)	NNT (CI)
			Antifungal agents	Control		
Death	All	24	14.7%	15.4%	5% (–11 to 18)	Not significant
Invasive infections	All	26	4.2%	8.6%	50% (36 to 61)	23 (17 to 35)
	Amphotericin	7	2.7%	7.5%	61% (24 to 80)	21 (13 to 63)
	Fluconazole	8	4.3%	11%	61% (43 to 73)	15 (11 to 24)
	Itraconazole	3	3.6%	7.2%	49% (4 to 73)	28 (15 to 334)
	Miconazole	2	5.3%	10%	48% (–31 to 80)	Not significant
					RRI (CI)	NNH
	Ketoconazole	6	6.3%	4.6%	32% (–32 to 154)	Not significant
					RRR (CI)	NNT (CI)
Colonization	All	22	31%	47%	36% (21 to 47)	7 (5 to 12)†
Use of rescue drug	All	20	44%	50%	12% (2 to 22)	19 (11 to 72)†

*Abbreviations defined in Glossary; RRI, RRR, NNT, NNH, and CI calculated from data in article using a fixed-effects model. Length of follow-up not reported.
†Statistically significant heterogeneity existed among trials; random-effects model was used.

COMMENTARY

IFIs cause considerable morbidity and mortality in cancer patients treated with cytoreductive chemotherapy (1). The risk factors for IFI include fungal colonization (2), prolonged neutropenia (2), chemotherapy-induced muscosal damage (3), BMT (4), and graft-versus-host disease (GVHD) (5). As a result, clinicians have embraced several strategies to curtail these life-threatening infections: prophylactic, preemptive, and empiric use of antifungal agents, as well as environmental air control.

Gøtzsche and Johansen have exhaustively reviewed the effect of antifungal agents in neutropenic patients. They included a heterogeneous population of chemotherapy-induced neutropenic patients with cancer, as well as recipients of autologous and allogeneic marrow transplantation. By mixing different populations of patients with varying risks for IFI, the effect of the antifungal agent on the incidence and mortality of IFI could also have been masked. Allogeneic marrow transplant recipients have a greater potential for IFI than autologous recipients. In fact, the risk for IFI in the former group extends beyond the neutropenic period, after marrow engraftment, because of GVHD. As a result, prophylaxis may be extended for prolonged periods beyond the neutropenic phase. The authors did not consider this key issue and evaluated heterogeneous populations, which may have influenced IFI risk and mortality, although they were cognizant of other sources of bias. As they acknowledge, early rescue therapy with a parenteral antifungal agent (usually an amphotericin B compound) may have diminished mortality.

A more perplexing issue is why 27 prophylactic and 3 empiric trials were combined. Most prophylactic trials use oral antifungal agents (22/27 trials in this review) because of ease of administration, while empiric rescue therapy is administered intravenously.

Antifungal therapy most certainly reduces the incidence of IFI. However, its effect on mortality requires a better understanding of which groups stand to benefit the most.

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References

1. **Bow EJ.** Br J Haematol. 1998;101(Suppl 1):1-4.
2. **Rotstein C, Bow EJ, Laverdiere M, et al.** Clin Infect Dis. 1999;28:331-40.
3. **Bow EJ, Loewn R, Cheang MS, Schacter B.** Clin Infect Dis. 1995;21:361-9.
4. **Goodrich JM, Reed EC, Mori M, et al.** J Infect Dis. 1991;164:731-40.
5. **Meyers JD.** Semin Oncol. 1990(3 Suppl 6);17:10-3.