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Part 4 Future perspectives

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There is no evidence that absorption is affected by food, gastric pH or SCT-associated mucositis. Although the oral suspension may have a more rapid effect on oral and oesophageal candidiasis than the capsule form, these two formulations are likely to be equally effective in SFI as they achieve similar plasma concentrations (Laufen *et al.* 1995). The half-life is 24 hours and potentially therapeutic plasma concentrations are reached 2–4 hours after a single oral dose, the concentration doubling within 6–10 days of continuous daily dosing. Therefore, if the drug is started at the same time as CT or conditioning for SCT, after 5–7 days of 200 mg daily (orally or intravenously) steady-state plasma concentrations are reached and systemic prophylaxis is available well before the onset of severe neutropenia. These are promising PK data for a potential SFI prophylactic agent in HM.

Clinical trial results show clearly that fluconazole is effective prophylaxis and treatment for *C. albicans* infections of the oropharynx (Winston *et al.* 1993; Schaffner & Schaffner 1995; Studena *et al.* 1995). However, because of excellent upper gut absorption, little fluconazole reaches the lower gut, increasing its colonisation by *Candida* spp. and, therefore, the risk of systemic candidiasis (Odds *et al.* 1989; Rosenberg-Arska 1991). Hence the need for the co-administration of oral, non-absorbable amphotericin B to decontaminate the lower gut.

In vitro susceptibility testing shows that fluconazole is active against *C. albicans* at an MIC of 4 µg/ml. It is variably active against *C. glabrata* depending on the degree of sensitivity of the strain and it is inactive against *C. krusei* (Rex *et al.* 1997). *Aspergillus* spp. are intrinsically resistant even at very high concentrations in vitro and this is confirmed in a small clinical series in which between 800 mg and 2 g daily of fluconazole failed to control aspergillus SFI (Anaissie *et al.* 1995). Therefore, one would expect effective prophylaxis against only *C. albicans* in HM patients given a daily dose of fluconazole that would achieve in vivo concentrations equivalent to the *albicans* MIC in vitro.

PK studies in normal subjects suggest that a sustained daily oral dose of 200 mg will be sufficient. In a study of 26 patients receiving conventional CT for HM, this daily dose gave a mean maximum concentration (C_{\max}) of 7.1 µg/ml (SD 2.27) at day seven and none of the patients' levels was less than 4 µg/ml (Ellis *et al.* 1997). The same dosing in a series of eleven SCT patients gave less reassuring results at day 13 with only six reaching a minimum concentration (C_{\min}) of over 4 µg/ml (mean 4.35, SEM 0.72) but at day 27 only one of seven remaining in the study had a C_{\min} of less than 4 mg/ml (El Yazigi 1997). These data suggest that *C. albicans* SFI prophylaxis may be more consistent in CT than in SCT patients. Comparison of the outcomes of RCTs is difficult because of differences in doses of fluconazole, in comparator arms, in types of patients included and in the size of populations studied. However, even without the sophistication of meta-analysis, a consistency of outcomes is apparent and there is a clear difference between the trials of CT (predominantly) patients and those for SCT (exclusively) patients.

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Table 7.6 Summary of randomised trials of empirical antifungal therapy

Study	Treatment arms	No.	Resolution of fever	Days to resolution of fever	Fungal infection	Hospital stay	Cost-benefit analysis	Deaths (fungal)
Pizzo <i>et al.</i> (1982)	Ampho B 0.5 mg/kg per day i.v. Antibiotic regimen	18 16	NA NA	6 8	1 5	25(N) 22(N)	NA NA	3(1) 5(2)
Wingard <i>et al.</i> (1987)	Placebo ± empirical Ampho B Early empirical miconazole ± empirical Ampho B	111 97	14 15	NA NA	8 1	NA NA	NA NA	20(4) 20(0)
Fainstein <i>et al.</i> (1987)	Ampho B 0.5–1 mg/kg per day Ketoconazole 200 mg q.d.s.	83 75	55 43	NA NA	14 15	NA NA	NA NA	NA NA
EORTC (1989)	Ampho B 0.6 mg/kg per day i.v. Antibiotic regimen	68 64	47 34	NA NA	1 4	NA NA	NA NA	11(0) 14(4)
Walsh <i>et al.</i> (1991)	Ampho B 0.5 mg/kg per day Ketoconazole 800 mg/kg per day	32 32	NA NA	3 4	4 6	NA NA	NA NA	7(3) 5(2)
Ellis <i>et al.</i> (1995)	Ampho B 0.5 mg/kg per day Fluconazole 8–4 mg/kg per day	25 16	21 8	7.7 11	3 6	NA NA	NA NA	6(2) 8(5)
Viscoli <i>et al.</i> (1996)	Ampho B 0.8 mg/kg per day Fluconazole 6 mg/kg per day	56 56	37 42	5 3	NA NA	NA NA	NA NA	2(0) 3(0)
Prentice <i>et al.</i> (1997)	Ampho B 1 mg/kg per day Liposomal Ampho 1 mg/kg per day Liposomal Ampho 3 mg/kg per day	102 118 118	49 68 75	7 8 10	2 3 2	NA NA NA	NA NA NA	18(0)

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