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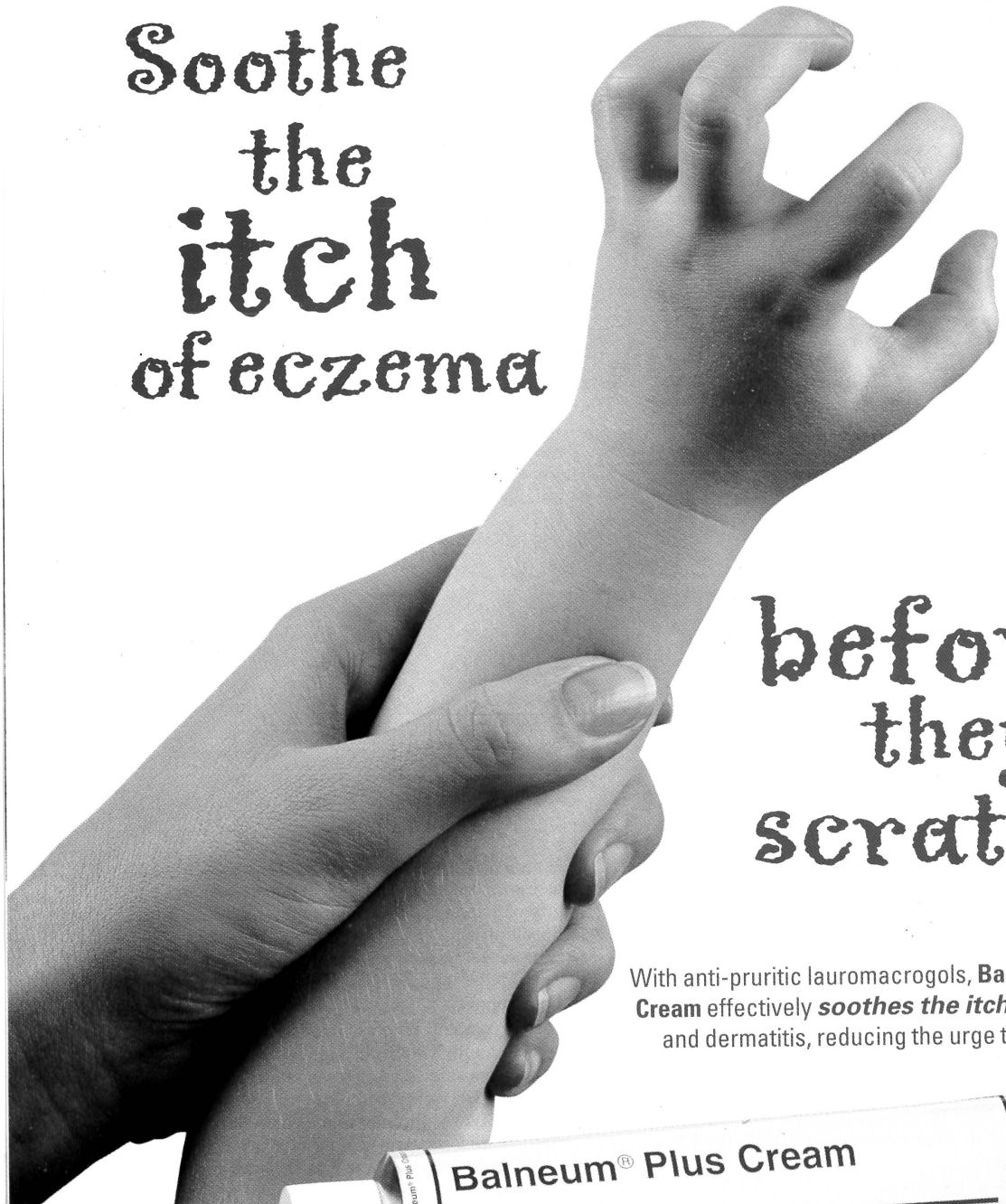

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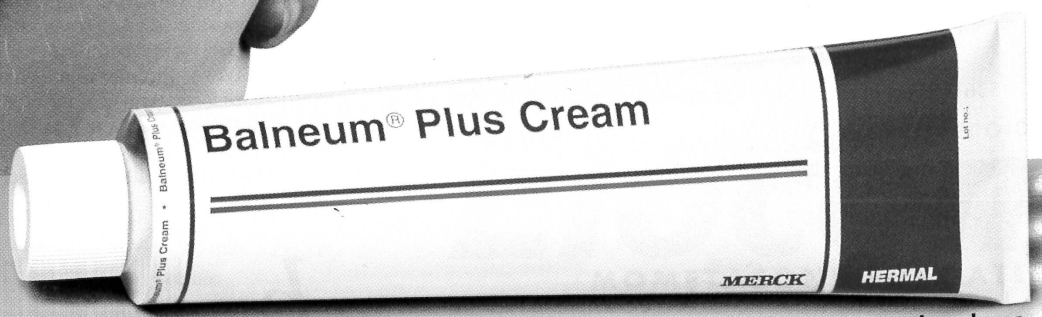

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Non-dermatophytes in onychomycosis of the toenails

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Summary A multicentre trial for the treatment of dermatophyte onychomycosis of the toenails with terbinafine was carried out in Australia and New Zealand. Between eight and 12 nail samples were obtained from each of the 118 patients in the 48-week trial, and each sample was investigated by direct microscopy and culture for dermatophyte and non-dermatophyte fungi. Patients were randomized to treatment with terbinafine at 250 mg/day or placebo for the first 12 weeks of the study, then non-responders were offered a 12-week course of terbinafine from week 28. All patients had a dermatophyte infection. In 42 patients (36%) microscopy and mycological culture identified dermatophytes alone. In the remaining 76 patients (64%), a non-dermatophyte mould or yeast was also isolated at some stage during the trial, but in only three patients did the same non-dermatophyte persist in two or more successive nail specimens. The presence of a fungal contaminant in addition to a dermatophyte had no apparent effect on the efficacy of treatment with terbinafine. We conclude that non-dermatophyte moulds and yeasts are generally found as contaminating organisms in dermatophyte onychomycosis, secondary to the dermatophytes, and that they do not influence the outcome of treatment.

Dermatophytes are the principal cause of onychomycosis, accounting for 90% of toenail infections and at least 50% of fingernail infections, 90% if paronychia is excluded. *Trichophyton rubrum* and *Trichophyton mentagrophytes* var. *interdigitale* are the dominant dermatophyte species involved. *Candida* is mainly associated with paronychia affecting the fingernails. The main non-dermatophyte moulds involved in onychomycosis as primary pathogens appear to be *Scopulariopsis* and *Scytalidium*, and such infections may account for between 1·5% and 6% of nail infections.[1–3] However, there is considerable controversy on the significance of non-dermatophyte moulds and yeasts when they are identified in the presence of a dermatophyte. It has been claimed that these so-called mixed infections are increasing in frequency, with important implications for patient management.[4] However, most information on the mycology of onychomycosis has been obtained either from cross-sectional epidemiology studies or from investigations of specific organisms in patients selected for clinical trials of therapeutic agents. There is little information on the complete mycological history of infection before, during and after therapy. We present data from repeated investigations in patients with onychomycosis who were treated with the antifungal agent terbinafine.[5]

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Methods

Patients were aged from 18 to 70 years with distal or total dermatophyte onychomycosis of at least one toenail, confirmed by mycological culture. They initially entered a randomized, double-blind, 12-week comparison of terbinafine (250 mg once daily) or matching placebo. At week 24, after a 12-week wash-out period, patients were classified as responders or non-responders. Non-responders were offered 12 weeks of terbinafine (250 mg once daily) from week 28. The trial was conducted in 11 centres in Australia and in two centres New Zealand, and the results have been published previously.[5]

Patients were seen at baseline and then at weeks 4, 8, 12, 16 and 24. The most severely affected toenail was assessed for efficacy. Response to 12 weeks treatment with terbinafine or placebo was assessed at week 24. Patients were classified as responders if they had a negative culture for a dermatophyte and the unaffected

Table 1. Mycology of a single toenail with a pure dermatophyte infection over 12 months

Week	Microscopy	Culture	Treatment
Baseline	++	*Trichophyton rubrum*	terbinafine 250 mg/day for 12 weeks
4	++	*Trichophyton rubrum*	
8	++	*Trichophyton rubrum*	
12	+	*Trichophyton rubrum*	
16	+	*Trichophyton rubrum*	
24	+	–	
28	+	–	
36	+	–	
48	–	–	

length of the toenail had increased by at least 3 mm from baseline. Responders and non-responders who refused a course of terbinafine in the second part of the trial were seen at weeks 28, 36 and 48. At each visit, the target toenail was assessed clinically and mycologically by direct microscopy and mycological culture.[5] Each patient had between eight and 12 consecutive nail specimens collected from the same nail allowing for an assessment of the fungal nail flora from 1321 nail specimens.

For the direct microscopic examination of nail scrapings a wet mount was made in 10% potassium hydroxide solution with Parker ink or Calcofluor white stain. For culture, specimens were inoculated on to Sabouraud's dextrose agar (SDA) containing chloramphenicol, gentamicin and cycloheximide (actidione). Duplicate cultures were also set up on SDA plates without cycloheximide.[6] All cultures were incubated at 26 °C for 4 weeks.

Results

There were 118 patients included in the trial, of whom 111 were available for assessment at week 24, and 107 were available for assessment at week 48. At the start of the trial, 96 (81%) patients were infected with *T. rubrum*, 19 (16%) with *T. mentagrophytes* var. *interdigitale*, two (2%) with *Trichophyton tonsurans* and one (1%) with *Epidermophyton floccosum*.

The typical mycological findings from a patient with a pure dermatophyte infection are shown in Table 1. The nail was initially diagnosed by microscopy and culture as being positive for *T. rubrum*. The patient was then randomized to receive terbinafine 250 mg/day for 12 weeks. Nail culture remained positive for a month after treatment, and fungal elements remained present for a further 4 months, although they were non-viable. At the end of the trial, the nails were clinically and mycologically cured. A similar result was recorded in 36% of the 118 patients, where a dermatophyte only was isolated, from the commencement of treatment to either the successful eradication of infection or the end of the study.

The other 64% of patients had an underlying dermatophyte infection with at least one non-dermatophyte mould or yeast isolated from one or more specimens during the study period. For example, the mycological findings in the nail of one of these patients are presented in Table 2. The only difference from the previous case is the appearance of some non-dermatophyte moulds, such as *Scopulariopsis*, *Curvularia* and *Penicillium*, as incidental contaminants. However, once again the treatment outcome was the same and the nail was clinically and mycologically cured at 12 months. The non-dermatophyte moulds and yeasts isolated as incidental contaminants from a study of 174 specimens collected from 76 patients, and their relative incidence, are reported in Table 3.

Significantly, only three (2·5%) of 118 patients had the same species of non-dermatophyte mould or yeast isolated from two or more consecutive specimens. One patient had *Scedosporium apiospermum* isolated on five consecutive occasions (Table 4), another had *Scopulariopsis brevicaulis* isolated on three consecutive occasions, and the third had *Candida famata* isolated of two consecutive occasions. It should also be noted that the fungal elements detected on direct microscopy of the nail specimens from these three patients were consistent with those of a dermatophyte (Table 4). Once again, the treatment outcome was the same and in all cases the nails were clinically and mycologically cured at 12 months following treatment with terbinafine.

Table 2. Mycology of a single toenail showing the occurrence of *Scopulariopsis*, *Curvularia* and *Penicillium* as incidental contaminants of an underlying dermatophyte infection

Week	Microscopy	Culture	Treatment
Baseline	++	*Trichophyton rubrum*	terbinafine 250 mg/day for 12 weeks
4	++	*Trichophyton rubrum*	
8	++	*Trichophyton rubrum*	
12	+	*Trichophyton rubrum*	
16	+	*Scopulariopsis*	
24	+	*Curvularia* and *Penicillium*	
28	+	–	
36	+	–	
48	–	–	

Discussion

Repeated samples of toenails affected by a dermatophyte onychomycosis revealed that a non-dermatophyte or

Table 3. Incidence of non-dermatophyte moulds and yeasts from nails of 118 patients with an underlying dermatophyte infection (data from 1321 nail specimens)

Genus	Number	Frequency
Cladosporium	38	2·9%
Alternaria	18	1·4%
Epicoccum	18	1·4%
Penicillium	17	1·3%
Aspergillus	12	0·9%
Curvularia	8	0·6%
Scopulariopsis	8	0·6%
Chrysosporium	5	0·4%
Fusarium	5	0·4%
Scedosporium	5	0·4%
Chaetomium	4	0·3%
Stemphylium	4	0·3%
Scytalidium	3	0·2%
Paecilomyces	3	0·2%
Drechslera	3	0·2%
Acremonium	2	0·15%
Geotrichum	2	0·15%
Ulocladium	2	0·15%
Beauveria	1	0·08%
Exophiala	1	0·08%
Graphium	1	0·08%
Stachybotrys	1	0·08%
Candida	10	0·7%
Rhodotorula	3	0·2%

yeast was isolated on a single occasion in almost two-thirds of patients. The occurrence of these organisms represent incidental contaminants associated with a non-sterile specimen. Weitzman and Summerbell[6] have also reported that the growth of non-dermatophytes is common from nails, but that successive sampling will rarely demonstrate the same contaminant. Although recognizing that the isolation of an organism does not prove it is the causative pathogen, Greer[4] claimed there is accumulating evidence of mixed infections in onychomycosis with important implications for the management of the disease. In this study, only three of 118 patients had the same non-dermatophyte isolated from two or more consecutive specimens. These three cases probably represent secondary colonization where the fungi concerned are utilizing nutrients available from the breakdown of keratin by the underlying dermatophyte. The overall mycological cure rate for patients treated with terbinafine in this trial was 94%.[5] This high cure rate suggests that transient, incidental contamination or secondary colonization with non-dermatophytes or yeasts had little impact on the therapeutic outcome.

Table 4. Mycology of a single toenail showing the occurrence of *Scedosporium apiospermum* as a secondary colonizer of an underlying dermatophyte infection

Week	Microscopy	Culture	Treatment
Baseline	+	*Trichophyton rubrum*	placebo for 12 weeks
4	+	*Scedosporium*	
8	+	*Trichophyton rubrum*	
12	+	*Graphium* sp.	
16	+	*Scedosporium*	
24	+	*Scedosporium*	
28	+	*Scedosporium*	terbinafine 250 mg/day for 12 weeks
36	–	*Scedosporium*	
40	–	–	
48	–	–	

An epidemiological survey in Britain confirmed that most cases of onychomycoses occur in the toenails rather than fingernails, and dermatophytes are the most important pathogens. *Trichophyton rubrum* was the most common cause, followed by *T. mentagrophytes* var. *interdigitale* and *E. floccosum*.[2] Our results support the predominance of *T. rubrum* and *T. mentagrophytes* var. *interdigitale* in toenail onychomycosis.

The role of non-dermatophyte moulds remains controversial. Traditionally they have been regarded as secondary pathogens of nails which are already diseased, although they may act as primary pathogens in a small number of cases. For example, non-dermatophytes such as *Scopulariopsis* and *Scytalidium* can opportunistically invade keratin that has already been degraded. When they are present it is usually with a dermatophyte and in an injured nail. Williams[2] stated that non-dermatophytes could account for 1·5%–6% of all onychomycoses, but their role as a causative agent is still very much a matter of debate and their interaction with dermatophytes, pre-existing disease and nail damage is still unclear. *Candida* and other yeasts can also be found as saprophytes in nail tissue, directly invading the nail plate only when host defences are disturbed, such as in immune suppression. The presence of a dermatophyte on direct microscopy or culture has long been accepted as evidence that it is the pathogen responsible for disease, even in mixed infections.[2] Weitzman and Summerbell[6] supported the view that dermatophytic fungi are still the main aetiological agents of onychomycosis and stressed that the growth of a non-dermatophyte on culture following a positive result on direct microscopy is not sufficient to diagnose a non-dermatophyte infection.

The longitudinal data from our trial, based on at least eight samples from each patient over 48 weeks, strongly

support the notion that non-dermatophytes and yeasts do not have a significant role in fungal infections of the toenail. Mixed infections, involving the persistence of a non-dermatophyte in two or more successive specimens, were very rare and probably represent secondary colonization. The fungi involved have questionable pathogenicity and are probably utilizing the products of dermatophytic keratin degradation as a nutrient source. Non-dermatophyte moulds and, less commonly, yeasts often appeared transiently as incidental contaminants, but they had no impact on the outcome of therapy with terbinafine.

Considering the strong evidence of the role of dermatophytes in onychomycosis and the common occurrence of incidental contaminants, it would be useful for clinicians if laboratory reports included a comment on the likely significance of a culture result, as well as the result itself. Repeat collections may also be necessary to detect the presence of a dermatophyte in nail specimens, as most contaminant fungi will overgrow or mask the presence of a dermatophyte in culture.

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