Efficacy of topical antifungal drugs in different dermatomycoses: a systematic review with meta-analysis

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Summary

Objective: To evaluate and compare the efficacy of topical antifungal drugs applied to the treatment of each dermatomycosis. **Methods:** A systematic review of randomized clinical trials, published in Portuguese, Spanish and English until July 2010, which compared the use of azole and allylamine antifungal drugs among themselves and with placebo in the treatment of cutaneous candidiasis and *T. versicolor, T. pedis, T. cruris* and *T. corporis* was performed. The efficacy outcomes evaluated were mycological cure at the end of treatment and sustained cure. **Results:** Of the 4,424 studies initially identified, 49 met the selection criteria and were included in the meta-analyses. The grouped efficacy data evidenced the superiority of antifungal drugs compared to placebo, regardless of the dermatomycosis under evaluation, with odds ratio values ranging from 2.05 (95% CI; 1.18-3.54) to 67.53 (95% CI; 11.43-398.86). Allylamines were better than azoles only for the outcome of sustained cure (OR 0.52 [95% CI; 0.31-0.89]). **Conclusion:** There is consistent evidence of the superiority of antifungal drugs over the use of placebo, and placebo-controlled studies are no longer justifiable. Allylamines maintain the mycological cure for longer periods compared to azole drugs. Given the significant cost difference among the classes, pharmacoeconomic analyses should be performed.

Keywords: Dermatomycoses; antimycotic drugs; meta-analysis; topical administration.

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Introduction

Dermatomycoses are the most widespread superficial fungal infections among human beings, being an important cause for morbidity. Although they rarely present risk to the life of patients, they may result in debilitating effects, affecting their quality of life[1-3].

The incidence of these diseases is increasing due to the higher number of immunocompromised patients and of recreation spaces, in which swimming pools and other fomites are shared[3]. The most frequent diseases are dermatophytoses or tineas (ringworms) infections resulting from fungi affecting the keratinized tissues of the skin, hair, and nails. Skin commensal yeasts, such as *Malassezia furfur* and *Candida* spp., are also important causative agents of dermatomycoses[4].

The diagnosis of these diseases is based on the combination of clinical and laboratory data. Clinical diagnosis should include physical examination of lesions and epidemiological history, while mycological diagnosis is mainly based on microorganism visualization in direct microscopy and growth in culture[4-6].

The treatment of these infections is different from that used in systemic infections, consisting in the primary use of antifungal topical formulations[7-8], which are sold over the counter in Brazil[9].

Given the shortage of systematic and quantitative review studies related to the treatment of dermatomycoses with topical antifungal drugs, and given that those already published are limited to the treatment of *Tinea pedis*[10,11], a quantitative systematic review was performed to determine the efficacy of topical antifungal drugs in the treatment of each dermatomycosis and to establish possible differences among pharmacological classes.

Methods

Search strategy and selection criteria

The research was conducted based on the recommendations of the Cochrane Collaboration for systematic reviews and meta-analyses[12]. A wide spectrum of strategies was used in the search for randomized clinical trials (RCT), and the descriptors were the names of azoles and allylamine antifungal drugs of interest (bifonazole, ketoconazole, clotrimazole, econazole, fenticonazole, flutrimazole, isoconazole, miconazole, naftifine, oxiconazole, sertaconazole, terbinafine, and tioconazole). The terms "vaginal", "vulvovaginal", and "oropharyngeal" were included in the search preceded by the Boolean term "NOT", and only studies that evaluated the topical use of these drugs were selected.

The search was performed in the MEDLINE, Cochrane Central Register of Controlled Trials, Embase, LILACS, and International Pharmaceutical Abstracts (IPA) databases, and included studies published up July 2010, in Portuguese, Spanish or English, which compared the use of topical antifungal drugs in treatment of dermatomycoses among themselves or with a placebo. Studies that did not restrict their evaluation scope to single type of dermatomycosis were excluded, including patients diagnosed with dermatophytoses or dermatomycoses in general. Furthermore, studies evaluating onychomycosis were excluded because this disease presents a very distinct pattern of treatment duration due to its chronic status.

The intervention consisted in any azole or allylamine topical antifungal drug, regardless of the dosage form, concentration, therapeutic regimen, and duration of the treatment. In each study, the clinical diagnosis for dermatomycosis should have been mycologically confirmed through the direct microscopy and/or fungal growth in culture technique.

The initial selection of studies, based on the evaluation of the title and summary, was performed by two independent proofreaders (IR and AS). Any discrepancy was resolved in a consensus meeting and, when necessary, in the presence of a third proofreader (CC).

Data extraction and quality assessment

The extraction of data from the selected studies was performed by the same independent proofreaders (IR and AS). The collected data consisted of patients' basic characteristics, evaluated dermatomycosis, interventions and controls, therapeutic regimen used, and efficacy data.

The efficacy results evaluated were mycological cure at the end of treatment, which included results of cure obtained at the end of the treatment, or up to seven days after its conclusion; and sustained cure, which included results of cure obtained after the treatment period, with a 14-day minimal interval without administration of the studied medications. In cases where more than one result of sustained cure was described, the one with the longest follow-up period was prioritized. For both efficacy results, the cure was confirmed through microscopy and/or culture. The clinical cure rate, due to its subjective nature, was not considered, and studies that only reported this result were excluded. Studies that only evaluated patients with *T. cruris* were added to those that included patients with diagnosis of *T. cruris* and *T. corporis*.

The methodological quality of each selected study was assessed through the scale of Jadad et al.[13], which takes into account aspects related to the randomization, blinding, losses, and withdrawals. Only studies that presented a minimum score of 3 were included. To assess the risk of bias, a tool made available by The Cochrane Collaboration, that analyzes the study in six domains, considering the following biases: selection, performance, detection, attrition, publication bias and other sources of biases, was used[12]. Thus, only good quality controlled and randomized clinical trials were included in the analyses, with evidence level 1a and grade of recommendation A[14].

Statistical analyses

For the efficacy results analyzed, the random effect model and inverse variance method was used to interpolate individual odds ratio (OR) results of the studies. The results were also expressed in absolute risk (AR), absolute risk reduction (ARR), and number needed to treat (NNT).

The existing heterogeneity among the selected studies was assessed through the inconsistency index (I^2), provided that an amount higher than 50% is indicative of high heterogeneity. In these cases, sensitivity analyses were conducted in order to identify whether the individual characteristics of each study could have influenced the results. Therefore, each study was hypothetically removed from the meta-analysis and its influence on the global result assessed. All analyses were performed through the software Review Manager 5.V.1.

Results

Systematic review

4,424 articles were retrieved, of which 4,183 were excluded after title and/or summary evaluation, and 95 after full evaluation. The main reasons that resulted in exclusion were noncompliance with the quality criteria proposed by Jadad, and the fact that many of them did not restrict their evaluation to a single type of dermatomycosis. Additionally, 97 were excluded because they were duplicated. Hence, 49 studies met the eligibility criteria and were included in the meta-analyses. Of these, data from 57 comparisons were extracted in a universe of 6,044 recruited patients. With respect to the basic characteristics of these patients, the weighted average age was 39.2 years, and 69.6% were male.

Tables 1 and 2 describe the characteristics of the studies included in the meta-analyses.

Critical quality assessment

Only medium to high quality studies were included, pursuant to the criteria of Jadad et al.[13]; an average score of 3.4 was found in the studies. In most studies selected, the information available in the articles related to the method used to generate the randomization sequence and allocation concealment was insufficient. However, the basic characteristics of the patients allocated to each group were homogenous, suggesting that the attribution of moderate risk of bias for this domain did not affect the reliability of the results found.

Efficacy results by evaluated dermatomycosis

Cutaneous candidiasis

Five studies were retrieved, which resulted in a total of 383 patients and six comparisons between topical antifungal drugs and placebo in the treatment of cutaneous candidiasis. Of these comparisons, four were established between placebo and the azoles miconazole 2%, clotrimazole 1%, econazole 1%, and bifonazole 1%, with a treatment period of 14 to 28 days. In the other two, the allylamine naftifine 1% was compared to placebo, with a 21-day treatment period.

For the outcome of mycological cure at the end of treatment, both meta-analyses results favored antifungal drugs. OR values of 10.06 (95% CI; 3.01-33.64), AR of 75%, ARR of 48%, and NNT of 2 were found in favor of the azoles and OR values of 67.53 (95% CI; 11.43-398.86), AR of 88%, ARR of 78%, and NNT of 1 favoring the allylamines when compared to placebo.

The I^2 of 35% found in the comparison established between azoles and placebo indicates the existence of moderate heterogeneity among the included results, being high (I^2 = 52%) between the studies selected to integrate the meta-analysis comparing allylamines and placebo. Although a high heterogeneity was found between the two included studies, they showed similar results favoring naftifine.

Only studies comparing naftifine with placebo showed results of sustained cure, and OR values of 37.14 (95% CI; 13.08-105.45), AR of 83%, ARR of 71%, and NNT of 1, favoring the use of allylamine. The heterogeneity was null among the selected studies (I^2 = 0%). The follow-up period was of two weeks after the end of therapy.

T. versicolor

Ten placebo-controlled studies, totaling 798 patients, evaluated the treatment of *T. versicolor*. Of these studies, data from eight comparisons established between placebo and the azoles clotrimazole 1%, bifonazole 1%, miconazole 2%, ketoconazole 2%, and econazole 1% were extracted, with a treatment period varying from two days, using the shampoo dosage form, to 28 days. Another four studies compared naftifine and terbinafibe, both at 1%, with placebo over treatment periods from seven to 28 days.

For the outcome of mycological cure at the end of treatment, the interpolation of six studies comparing azoles with placebo resulted in an OR of 20.11 (95% CI; 9.07-44.59), AR of 89%, ARR of 54%, and NNT of 2, favoring antifungal drugs. When grouping the results of three studies comparing allylamines with placebo, the OR value obtained was 2.05 (95% CI; 1.18-3.54), AR of 47%, ARR of 17%, and NNT of 6, favoring allylamines. The inconsistency index observed among the interpolated studies was null (I^2 = 0%) or low (I^2 = 23%).

For the outcome of sustained cure, the combined data from seven studies comparing azoles with placebo resulted in an OR of 12.61 (95% CI; 5.23-30.41), AR of 83%, ARR of 59%, and NNT of 2, favoring azoles. The value of I^2 was 30% indicating moderate heterogeneity among the studies. The follow-up period was from two to six weeks after the end of the therapy. The grouping of

Table 1 – Characteristics of the studies included in the meta-analyses: azole and allylamine drugs versus placebo

Author, year	Jadad score	n total	Dermatomycosis evaluated	Intervention	Dosage form	Therapeutic regimen	Duration of the treatment (days)	Total follow-up period (days)	Assessed outcomes (Cure)
Astorga, 1989[15]	4	59	Candidiasis	Naftifine 1%	Cream	Twice a day	21	35	Mic/Sust
Bagatell, 1991a[16]	3	88	*T. pedis*	Naftifine 1%	Cream	Twice a day	28	42	Mic/Sust
Bagatell, 1991b[16]	3	228	*T. pedis*	Naftifine 1%	Cream	Twice a day	28	42	Mic/Sust
Berman, 1992[17]	3	165	*T. pedis*	Terbinafine 1%	Cream	Twice a day	7	42	Mic/Sust
Budimulja, 2001[18]	3	120	*T. cruris* and *T. corporis*	Terbinafine 1%	Cream	Once a day	7	56	Sustained
Cullen, 1977[19]	3	30	Candidiasis	Miconazole 2%	Lotion	Twice a day	14	28	Mycological
Cullen, 1984a[20]	3	26	Candidiasis	Clotrimazole 1%	Cream	Twice a day	14 to 21	42 to 49	Mycological
Cullen, 1984b[20]	3	23	Candidiasis	Econazole 1%	Cream	Twice a day	14 to 21	42 to 49	Mycological
Daily, 1985[21]	3	91	*T. pedis*	Econazole 1%	Cream	Twice a day	28 to 42	56 to 70	Mic/Sust
Duncan, 1975[22]	3	150	*T. pedis*	Miconazole 2%	Cream	Twice a day	28	56	Mic/Sust
Ellis, 1989a[23]	4	178	*T. pedis*	Oxiconazole 1%	Cream	Once a day	28	42	Mic/Sust
Ellis, 1989b[23]	4	179	*T. pedis*	Oxiconazole 1%	Cream	Twice a day	28	42	Mic/Sust
Evans, 1991[24]	3	86	*T. pedis*	Terbinafine 1%	Cream	Once a day	14	42	Mic/Sust
Evans, 1992[25]	3	76	*T. cruris* and *T. corporis*	Terbinafine 1%	Cream	Once a day	7	28	Mic/Sust
Faergemann, 1997[26]	3	61	*T. versicolor*	Terbinafine 1%	Emulsion – gel	Once a day	7	56	Mic/Sust
Gentles, 1975[27]	4	56	*T. pedis*	Miconazole 2% Miconazole 1%	Cream Powder	Once a day Twice a day	28	28	Mycological
Greer, 1990[28]	3	23	*T. cruris*	Terbinafine 1%	Cream	Twice a day	14	28	Mic/Sust
Hollmen, 2002[29]	3	101	*T. pedis*	Terbinafine 1%	Emulsion – gel	Once a day	7	56	Sustained
James, 2007a[30]	4	56	*T. pedis*	Terbinafine 1%	Emulsion – gel	Once a day	5	42	Mic/Sust
James, 2007b[30]	4	55	*T. pedis*	Terbinafine 3%	Emulsion – gel	Once a day	5	42	Mic/Sust
Korting, 2001[31]	3	100	*T. pedis*	Terbinafine 1%	Cream	Once a day	7	56	Sustained
Lalosevic, 1984a[32]	4	129	Candidiasis	Bifonazole 1%	Cream	Once a day	28	42	Mycological
Lalosevic, 1984b[32]	4	134	Candidiasis	Bifonazole 1%	Cream	Twice a day	28	42	Mycological
Lebwohl, 2001a[33]	4	153	*T. pedis*	Terbinafine 1%	Solution	Twice a day	7	56	Mycological
Lebwohl, 2001b[33]	4	66	*T. cruris* and *T. corporis*	Terbinafine 1%	Solution	Once a day	7	28	Mycological
Millikan, 1990[34]	3	30	*T. cruris*	Terbinafine 1%	Cream	Twice a day	14	28	
Montoya, 1985a[35]	3	48	*T. versicolor*	Clotrimazole 1%	Cream	Twice a day	28	42	Mic/Sust
Montoya, 1985b[35]	3	44	*T. versicolor*	Naftifine 1%	Cream	Twice a day	28	42	Mic/Sust
Mora, 1984[36]	4	43	*T. versicolor*	Bifonazole 1%	Cream	Once a day	14	28	Mic/Sust
Ortiz, 1978a[37]	3	100	*T. pedis*	Miconazole 2%	Cream	Twice a day	28	56	Mycological
Ortiz, 1978b[37]	3	50	*T. versicolor*	Miconazole 2%	Cream	Twice a day	14	28	Mic/Sust
Ortonne, 2006[38]	3	324	*T. pedis*	Terbinafine 1%	FFS*	Single dose	–	–	Sustained
Quiñones, 1980a[39]	3	41	*T. versicolor*	Miconazole 2%	Cream	Once a day	14	28	Sustained
Quiñones, 1980b[39]	3	51	*T. versicolor*	Econazole 1%	Cream	Once a day	14	28	Sustained
Savin, 1986[40]	3	101	*T. versicolor*	Ketoconazole 2%	Cream	Once a day	14	56	Mic/Sust
Savin, 1990[41]	3	27	*T. pedis*	Terbinafine 1%	Cream	Twice a day	28	42	Mic/Sust
Savin, 1999[42]	3	152	*T. versicolor*	Terbinafine 1%	Solution	Twice a day	7	56	Mic/Sust
Savin, 2006[43]	3	588	*T. pedis*	Sertaconazole 2%	Cream	Twice a day	28	42	Mic/Sust
Segal, 1999a[44]	4	20	*T. versicolor*	Bifonazole 1%	Shampoo	Once a day	2	42	Mic/Sust
Segal, 1999b[44]	4	20	*T. versicolor*	Bifonazole 1%	Shampoo	Once a day	7	42	Mic/Sust
Smith, 1977[45]	4	82	*T. pedis*	Clotrimazole 1%	Solution	Twice a day	28 to 42	28 to 42	Mycological
Smith, 1990a[46]	3	23	*T. pedis*	Terbinafine 1%	Cream	Twice a day	28	42	Mic/Sust
Syed, 2000[47]	4	40	*T. pedis*	Terbinafine 1%	Cream	Once a day	10	308	Mic/Sust
Van Heerden, 1997[48]	3	83	*T. cruris* and *T. corporis*	Terbinafine 1%	Emulsion – gel	Once a day	7	56	Mic/Sust
Vermeer, 1997[49]	3	115	*T. versicolor*	Terbinafine 1%	Solution	Twice a day	7	56	Sustained
Vicik, 1984[50]	4	148	*T. versicolor*	Econazole 1%	Cream	Once a day	14 to 21	14 to 21	Mycological
Zaias, 1988[51]	3	60	Candidiasis	Naftifine 1%	Cream	Twice a day	21	35	Mic/Sust

FFS, film forming solution; Mic, mycological; Sust, sustained.

Table 2 – Characteristics of the studies included in the meta-analyses: allylamines versus azoles

Author, year	Jadad Score	n total	Dermatomycosis evaluated	Intervention 1	Duration of the treatment (days)	Total follow-up period (days)	Intervention 2	Duration of the treatment (days)	Total follow-up period (days)	Evaluated outcomes (Cure)
Ablon, 1996a[52]	3	66	*T. pedis*	Terbinafine cream 1% once a day	14	42 to 70	Oxiconazole lotion 1% once a day	14	42 to 70	Mic/Sust
Ablon, 1996b[52]	3	66	*T. pedis*	Naftifine cream 1% once a day	14	42 to 70	Oxiconazole lotion 1% once a day	14	42 to 70	Mic/Sust
Aste, 1991[53]	3	40	*T. versicolor*	Terbinafine cream 1% twice a day	22	36	Bifonazole cream 1% twice a day	26	40	Mycological
Bergstresser, 1993[54]	3	193	*T. pedis*	Terbinafine cream 1% twice a day	7	84	Clotrimazole cream 1% twice a day	28	84	Sustained
Budimulja, 1998[55]	4	185	*T. cruris*	Terbinafine cream 1% once a day	7	56	Bifonazole cream 1% once a day	21	56	Mic/Sust
Evans, 1993[56]	5	256	*T. pedis*	Terbinafine cream 1% twice a day	7	42	Clotrimazole cream 1% twice a day	28	42	Mic/Sust
Irvine, 1990[57]	5	57	*T. pedis*	Naftifine cream 1% twice a day	28 to 42	28 to 42	Clotrimazole cream 1% twice a day	28 to 42	28 to 42	Mycological
Leenutaphong, 1999[58]	3	48	*T. pedis*	Terbinafine cream 1% once a day	7	70	Miconazole cream 2% twice a day	28	70	Mic/Sust
Millikan, 1988[59]	4	126	*T. cruris* and *T. corporis*	Naftifine cream 1% twice a day	28	42	Econazole cream 1% twice a day	28	42	Mic/Sust
Montoya, 1985c[35]	3	48	*T. versicolor*	Naftifine cream 1% twice a day	28	42	Clotrimazole cream 1% twice a day	28	42	Mic/Sust
Sanchez- Carazo, 1994[60]	3	43	*T. pedis*	Terbinafine cream 1% once a day	28	42	Bifonazole cream 1% once a day	28	42	Mic/Sust
Schopf, 1999[61]	4	699	*T. pedis*	Terbinafine solution 1% twice a day	7	56	Clotrimazole solution 1% twice a day	28	56	Mic/Sust
Smith, 1990b(1)[62]	3	160	*T. pedis*	Naftifine cream 1% once a day	28	42	Clotrimazole cream 1% twice a day	28	42	Mic/Sust
Smith, 1990b(2)[62]	3	121	*T. pedis*	Naftifine cream 1% twice a day	28	42	Clotrimazole cream 1% twice a day	28	42	Mic/Sust
Wahid, 1997[63]	3	87	*T. pedis*	Terbinafine cream 1% once a day	14	56	Bifonazole cream 1% once a day	14	56	Sustained

Mic, mycological; Sust, sustained.

four studies comparing allylamines with placebo showed an OR of 6.07 (95% CI; 2.19-16.86), AR of 75%, ARR of 45%, and NNT of 2, favoring allylamine drugs. High heterogeneity among the included studies was detected ($I^2 = 74\%$). However, after the hypothetical removal of the meta-analysis by Montoya[35], responsible for the high heterogeneity, the amount of I^2 decreased to zero and the efficacy result remained statistically favorable to allylamines. The follow-up period was from two to seven weeks after the end of the treatment.

T. pedis

Nineteen studies were found, in which 1,937 patients were recruited, comparing azole and allylamine antifungal drugs with placebo to treat *T. pedis*, being, therefore, the most evaluated dermatomycosis. Of these, seven studies compared the azoles econazole 1%, miconazole 2%, oxiconazole 1%, sertaconazole 2%, and clotrimazole 1% with placebo, with atreatment period of 28 to 42 days. The 12 remaining studies compared the allylamines naftifine 1% and terbinafine 1% and 3% with placebo, with a treatment period varying from one day, in case of film forming solution, which requires a single dose, up to 28 days.

For the outcome of mycological cure at the end of treatment, azoles and allylamines showed superiority when compared to placebo. The grouping of seven studies comparing azoles with placebo resulted in an OR of 5.54 (95% CI; 3.01-10.19), AR of 72%, ARR of 36%, and NNT of 3, with value of I^2 of 71%, indicating high heterogeneity among the included studies. With the hypothetical removal of the study by Ortiz[37] from the meta-analysis, the value of I^2 became null and the result remained statistically favorable to azoles. When nine studies comparing allylamines with placebo were interpolated, an OR of 5.87 (95% CI; 2.46-14.01), AR of 63%, ARR of 35%, and NNT of 3 were obtained, with a value of I^2 of 81%. With the hypothetical withdrawal of the studies identified as responsible for the high heterogeneity from the meta-analysis, the value of I^2 decreased and the result remained favorable to allylamines.

Azoles and allylamines were also better than placebo in the outcome of sustained cure; an OR of 6.64 (95% CI; 4.65-9.48), AR of 73%, ARR of 44%, and NNT of 2 was found when four studies comparing azoles with placebo were grouped, with follow-up period of two to four weeks after the end of the therapy. When grouping 11 studies comparing allylamines with placebo, with follow-up period of two to 12 weeks after the end of the treatment, an OR of 14.22 (95% CI; 9.49-21.32), AR of 78%, ARR of 56%, and NNT of 2 were obtained. The inconsistency index observed among the interpolated studies was null (I^2 = 0%) or low (I^2 = 23%).

T. cruris and *T. corporis*

On the evaluation of the treatment of *T. cruris* and *T. corporis*, six studies were retrieved, totalling 298 patients, all comparing terbinafine 1% with placebo, with a short period of treatment, from seven to 14 days, and follow-up period from two to seven weeks after the end of the therapy.

For the outcome of mycological cure at the end of treatment, the grouping of five studies resulted in an OR of 6.40 (95% CI; 2.64-15.49), an AR of 48%, ARR of 33%, and NNT of 3. The I^2 found was 6%. For the outcome sustained cure, the sum of the data from five studies resulted in an OR of 14.43 (95% CI; 7.62-27.33), AR of 85%, ARR of 58%, and NNT of 2, with a null value of I^2; therefore, terbinafine was superior to placebo in both analyzed outcomes.

Efficacy results of azoles versus allylamines

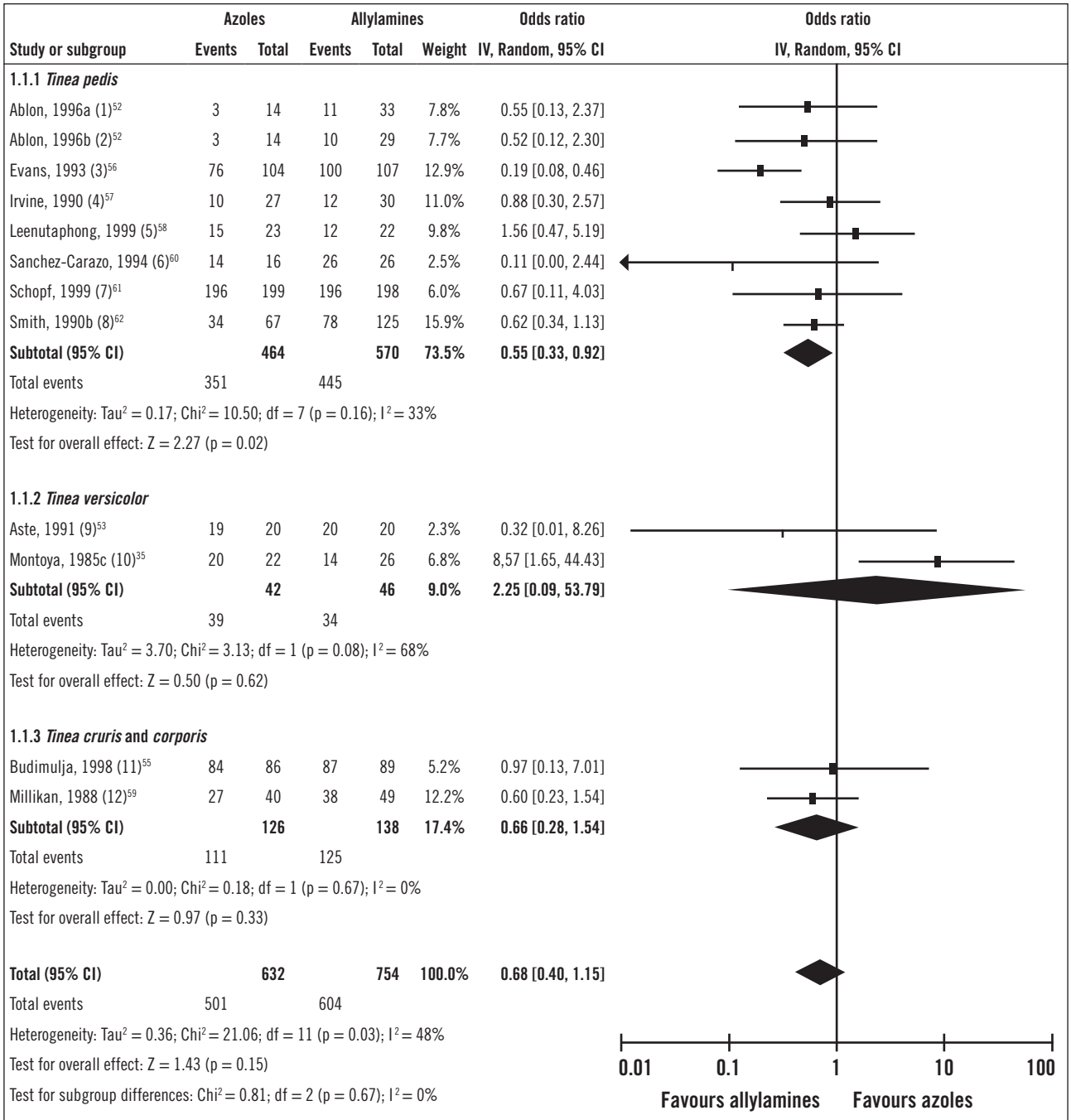
Fourteen studies comparing azoles to allylamine drugs in the treatment of dermatomycoses were retreived. Of these, ten evaluated patients were diagnosed with *T. pedis*, two with *T. versicolor*, and two with *T. cruris* and *T. corporis*. Figure 1 shows the results of the meta-analyses of azoles versus allylamines for each dermatomycosis evaluated.

For the outcome of mycological cure at the end of treatment, eight studies comparing the azoles oxiconazole 1%, clotrimazole 1%, miconazole 2%, and bifonazole 1% with naftifine and terbinafine, both at 1%, in the treatment of *T. pedis* were grouped. The value of OR obtained was statistically favorable to the use of allylamines (0.55 [95% CI; 0.33-0.92]), with AR of 78%, ARR of 2%, and NNT of 41. The I^2 value of 33% indicates moderate heterogeneity among the selected studies, validating the quality of the evidence found.

For the same outcome, when two studies comparing bifonazole and clotrimazole with terbinafine and naftifine, all at 1%, in the treatment of *T. versicolor* were grouped, a non-statistically significant OR value of 2.25 (95% CI; 0.09-53.79) was obtained, which was favorable to azoles, with values of AR of 93%, ARR of 19%, and NNT of 5. The value of I^2 was high (68%), as the results of the studies included were contradictory. In the study by Montoya[35], there was an impressive result in favor of azoles, while in the study by Aste[53], no difference was detected between the classes. The sum of the results of two studies evaluating the treatment of *T. cruris* and *T. corporis* also resulted in an not statistically significant OR of 0.66 (95% CI; 0.28-1.54), however it was favorable to allylamines, with AR of 91%, ARR of 2%, NNT of 40, and I^2 of 0%. The global result of the meta-analysis (0.68 [95% CI; 0.40-1.15]) did not show any difference between azoles and allylamines, not evidencing superiority of one class over the other.

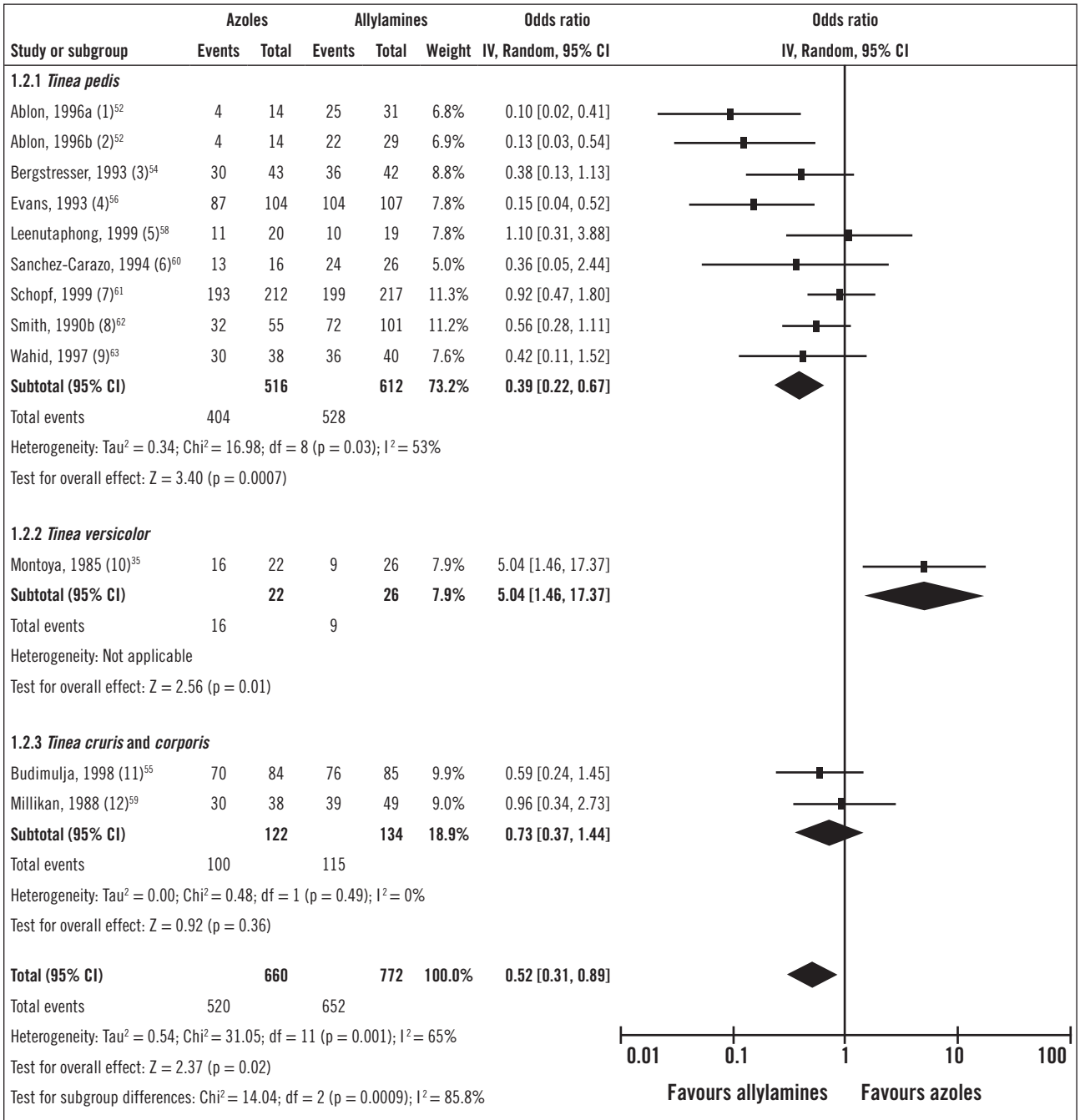
For the outcome of sustained cure, the grouping of nine studies evaluating the treatment of *T. pedis* resulted in an OR statistically favorable to the use of allylamines (0.39 [95% CI; 0.22-0.67]), with AR of 86%, ARR of 8%, and NNT of 13, however with a high heterogeneity among the selected studies (I^2 = 53%). When Ablon's study[52] was hypothetically removed from the meta-analysis, the heterogeneity became moderate and the result remained favorable to allylamines.

Only one study comparing clotrimazole to naftifine in the treatment of *T. versicolor* was retrieved, obtaining an OR of 5.04 (95% CI; 1.46-17.37), AR of 73%, ARR of 38%, and NNT of 3, favoring the azole clotrimazole. The interpolation of two studies comparing azoles and allylamines



(1) Oxiconazole lotion 1% once a day versus terbinafine cream 1% once a day for 14 days in the treatment of *T. pedis*
(2) Oxiconazole lotion 1% once a day versus naftifine gel 1% once a day for 14 days in the treatment of *T. pedis*
(3) Clotrimazole cream 1% twice a day for 28 days versus terbinafine cream 1% twice a day for seven days in the treatment of *T. pedis*
(4) Clotrimazole cream 1% twice a day versus naftifine cream 1% twice a day for 28 to 42 days in the treatment of *T. pedis*
(5) Miconazole cream 2% twice a day for 28 days versus terbinafine cream 1% once a day for seven days in the treatment of *T. pedis*
(6) Bifonazole cream 1% once a day versus terbinafine cream 1% once a day for 28 days in the treatment of *T. pedis*
(7) Clotrimazole solution 1% twice a day for 28 days versus terbinafine solution 1% twice a day for seven days in the treatment of *T. pedis*
(8) Clotrimazole cream 1% twice a day versus naftifine cream 1% once and twice a day for 28 in the treatment of *T. pedis*
(9) Bifonazole cream 1% twice a day for 26 days versus terbinafine cream 1% twice a day for 22 days in the treatment of *T. versicolor*
(10) Clotrimazole cream 1% twice a day versus naftifine cream 1% twice a day for 28 days in the treatment of *T. versicolor*
(11) Bifonazole cream 1% once a day for 21 days versus terbinafine cream 1% once a day for 7 seven in the treatment of *T. cruris*
(12) Econazole cream 1% twice a day versus naftifine cream 1% twice a day for 28 days in the treatment of *T. cruris* and *T. corporis*.

Figure 1A – Comparative efficacy of azoles versus allylamines. Meta-analyses of azoles versus allylamines for each dermatomycosis under evaluation. Mycological cure at the end of treatment.



(1) Oxiconazole lotion 1% once a day versus terbinafine cream 1% once a day for 14 days in the treatment of *T. pedis*. Follow-up for eight weeks.
(2) Oxiconazole lotion 1% once a day versus naftifine gel 1% once a day for 14 days in the treatment of *T. pedis*. Follow-up for eight weeks.
(3) Clotrimazole cream 1% twice a day for 28 days versus terbinafine cream 1% twice a day for seven days in the treatment of *T. pedis*. Follow-up for eight weeks.
(4) Clotrimazole cream 1% twice a day for 28 days versus terbinafine cream 1% twice a day for seven days in the treatment of *T. pedis*. Follow-up for two weeks.
(5) Miconazole cream 2% twice a day for 28 days versus terbinafine cream 1% once a day for seven days in the treatment of *T. pedis*. Follow-up for six weeks.
(6) Bifonazole cream 1% once a day versus terbinafine cream 1% once a day for 28 days in the treatment of *T. pedis*. Follow-up for two weeks.
(7) Clotrimazole solution 1% twice a day for 28 days versus terbinafine solution 1% twice a day for seven days in the treatment of *T. pedis*. Follow-up for four weeks.
(8) Clotrimazole cream 1% twice a day versus naftifine cream 1% once and twice a day for 28 in the treatment of *T. pedis*. Follow-up for two weeks.
(9) Bifonazole cream 1% once a day versus terbinafine cream 1% once a day for 14 days in the treatment of *T. pedis*. Follow-up for six weeks.
(10) Clotrimazole cream 1% twice a day versus naftifine cream 1% twice a day for 28 days in the treatment of *T. versicolor*. Follow-up for two weeks.
(11) Bifonazole cream 1% once a day for 21 days versus terbinafine cream 1% once a day for seven days in the treatment of *T. cruris*. Follow-up for five weeks.
(12) Econazole cream 1% twice a day versus naftifine cream 1% twice a day for 28 days in the treatment of *T. cruris* and *T. corporis*. Follow-up for two weeks.

Figure 1B – Comparative efficacy of azoles versus allylamines. Meta-analyses of azoles versus allylamines for each dermatomycosis under evaluation. Sustained cure.

in the treatment of *T. cruris* and *T. corporis* resulted in an OR of 0.73 (95% CI; 0.37-1.44), not showing a statistically significant difference of efficacy between the classes.

However, the result was favorable to allylamines, with AR of 86%, ARR of 4%, and NNT of 26, and I^2 of 0%. The global result of the meta-analysis (0.52 [95% CI; 0.31-0.89]) presented a difference between the pharmacological classes evaluated, evidencing superiority by the allylamines compared to azoles, even with the hypothetical withdrawal of Montoya's study[35], responsible for the high heterogeneity (I^2 = 65%).

Discussion

Dermatomycoses are the skin diseases that most commonly affect people worldwide, for which the first-line therapeutic strategy is the use of topical antifungal drugs[7]. While the popular use of these drugs prove their value in reducing the signs and symptoms of these infections, scientifically speaking, uncertainties with respect to the best therapy to be adopted in each case predominate, as a good part of the published clinical trials are small sized and have placebo as a comparator, and systematic review studies with meta-analysis are rare. Only two systematic reviews with meta-analyses can be found in the literature related to the treatment of dermatomycoses with topical antifungal drugs, both limited to the treatment of *T. pedis*[10-11]. In this research, all azole and allylamine antifungal drugs were compared among themselves and with placebo in the treatment of any dermatomycosis.

In this systematic review, 144 articles were fully evaluated, and 49 were selected to compose the meta-analyses. Of the 95 articles excluded, 35 failed to meet the quality criteria proposed by Jadad[13], and 26 did not define a specific dermatomycosis diagnosis. In the aggregate, 6,044 patients were randomly designated to receive placebo or one of the 13 antifungal drugs, with a predominance of young males.

The meta-analyses' results demonstrate that there is consistent evidence of the superiority of topical antifungal drugs over placebo, irrespectively of the drug evaluated, pharmacological class, dosage form, concentration, therapeutic regimen adopted, duration of the treatment, diagnosed dermatomycosis, and efficacy outcome taken into consideration. These findings are consistent with those found in the systematic reviews by Crawford[10] and Hart[11]; the superiority of all antifungal drugs compared to placebo in the treatment of *T. pedis* was detected.

Some meta-analyses presented high values of I^2 (> 50%), indicating inconsistency in the results of the included studies. However, after some sensitivity analyses, including the hypothetical removal from the meta-analysis of the studies considered responsible for the high heterogeneity mentioned, the results remained close to the ones found prior to the removal of the studies, maintaining their statistical significance. This shows that the variation of effects in the collected data upon several primary studies did not change the final measure of effect. These findings are comparable to those found in the systematic review by Crawford[10], whose meta-analyses also showed high heterogeneity among the selected studies.

Accordingly, given the strength of the evidences found, clinical trials controlled by placebo evaluating topical antifungal drugs in the treatment of dermatomycoses are no longer justifiable; only clinical trials comparing two active treatments are reccomended. Crawford et al., in 2008, published an article confirming that there is enough evidence to recommend the abandonment of trials controlled by placebo evaluating topical antifungal drugs in the treatment of *T. pedis*[64].

With respect to the comparisons made between antifungal classes, in Crawford's study, 11 studies comparing azoles with allylamines were selected and the result found was statistically favorable to allylamines, with difference between the classes detected in the period of six weeks following the beginning of the treatment and maintained in more extensive follow-up periods[10].

The same result favoring the use of allylamines was obtained in the study developed by Hart in 1999; however, a publication bias was detected. Of the 12 studies that integrated the meta-analysis, eight favored the allylamines, all published in English. The four additional studies did not show significant differences between the evaluated classes, all published in other languages[11].

In this research, for the outcome of mycological cure at the end of treatment, a statistically significant difference was found between the classes, favoring allylamines only in the treatment of *T. pedis*, which is consistent with the findings of Hart and Crawford[10-11]. When the results obtained for each dermatomycosis were aggregated, no difference of efficacy between the classes was identified.

For the outcome of sustained cure, once again allylamines were better compared to azoles in the treatment of *T. pedis*. For the treatment of *T. versicolor*, the azole clotrimazole was statistically better than naftifine but this result arose from a single clinical trial. The global result of the meta-analysis was statistically favorable to allylamines, even after sensitivity analyses. This superiority of the allylamines in the general result is due to the greater emphasis on studies involving *T. pedis* in the total meta-analysis. With the currently available evidence, it is not possible to state the superiority of allylamines with respect to azoles for other dermatomycoses.

The impressive maintenance of the cure after the end of the therapy can be supported by the lipophilic and keratinophilic characteristics of allylamines, enabling them to remain pharmacologically active in the skin even after the

suspension of the treatment. The fungicidal mechanism of action of allylamines, opposed to the fungistatic mechanism of the azole drugs, may also have contributed to better responses obtained with the usage of this class[4].

Due to the difference of cost between azole and allylamine drugs, the incorporation of economic outcomes into the systematic review, such as the performance of cost-effectiveness analyses, shall define the therapeutic option that presents the best clinical results per currency unit invested, representing the most effective alternative to each clinical condition taken into consideration.

Conclusion

The results found show consistent evidence of the superiority of antifungal drugs with respect to placebo in the treatment of any clinical form of dermatomycosis. Through meta-analyses of direct comparisons, a difference between azoles and allylamines in the treatment of *T. pedis* was detected; the result was favorable to allylamines for both cure outcomes. For the outcome of sustained cure, the global result of the meta-analysis shows that allylamines are better than azoles, nevertheless, the results have a high level of evidence only for *T. pedis*. There are no clinical trials of good methodological quality comparing azoles and allylamines in the treatment of cutaneous candidiasis.

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