Systemic antifungal therapy for tinea capitis in children: An abridged Cochrane Review

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Abstract

Background: The comparative efficacy and safety profiles of systemic antifungal drugs for tinea capitis in children remain unclear.

Objective: To assess the effects of systemic antifungal drugs for tinea capitis in children.

Methods: We used standard Cochrane methodological procedures.

Results: We included 25 randomized controlled trials (RCTs) with 4449 participants. Terbinafine and griseofulvin had similar effects for children with mixed *Trichophyton* and *Microsporum* infections (risk ratio [RR] 1.08, 95% confidence interval [CI] 0.94 to 1.24). Terbinafine was better than griseofulvin for complete cure of *T. tonsurans* infections (RR 1.47; 95% CI 1.22 to 1.77); griseofulvin was better than terbinafine for complete cure of infections caused solely by *Microsporum* species (RR 0.68; 95% CI 0.53 to 0.86). Compared with griseofulvin or terbinafine, itraconazole and fluconazole had similar effects against *Trichophyton* infections

Limitations: All included studies were at unclear or high risk of bias. Lower quality evidence resulted in a lower confidence in the estimate of effect. Significant clinical heterogeneity existed across studies.

Conclusions: Griseofulvin or terbinafine are both effective; terbinafine works better for *T. tonsurans* and griseofulvin for *M. canis* infections. Itraconazole and fluconazole are alternative but not optimal choices for *Trichophyton* infections. Optimal regimens of antifungal agents need further studies.

Keywords: Tinea capitis; children; systemic antifungal therapy; systematic review; Cochrane; treatment

CAPSULE SUMMARY

- Systemic antifungal therapy is the key intervention for tinea capitis.
- Griseofulvin and terbinafine are the first-line agents of choice; terbinafine and griseofulvin are better for *Trichophyton tonsurans* and *Microsporum canis*, respectively. Itraconazole and fluconazole are alternative treatments.
- Optimal regimens of antifungal agents remain to be elucidated.

INTRODUCTION

Tinea capitis is caused by dermatophyte fungi (usually *Trichophyton* or *Microsporum* species; e.g. *T. tonsurans*, *T. mentagrophytes*, *T. violaceum*, *M. canis*, and *M. audouini*, etc.). [1] It affects healthy preadolescent children and rarely occurs in adults., [1] It is common in countries of all income levels around the world; however, the prevalence varies across study populations within different geographical areas. [2] A fungal kerion describes an abscess-like mass, which if left untreated can lead to scarring and permanent hair loss.

Antifungal agents are the primary interventions for treating tinea capitis (e.g., griseofulvin, terbinafine, ketoconazole, fluconazole, and itraconazole). They are widely used in clinical practice. [1, 3] The comparative efficacy and safety profiles for these agents with different dosages or durations of treatment remain unclear. We conducted this literature review to address the efficacy and safety of systemic antifungal drugs for tinea capitis in children.

METHODS

Our analysis is based on a Cochrane review most recently updated in the Cochrane Library 2016, issue 5 (www.thecochranelibrary.com). [4] Full details of the methods and all the included studies are available from the Cochrane review.

Inclusion criteria

We included randomized controlled trials (RCTs) that were conducted in children with

normal immunity and with tinea capitis confirmed by microscopy, growth of dermatophytes in culture or both. All regimens of systemic antifungal therapies for tinea capitis were included.

Searches

We searched the following databases up to November 2015: MEDLINE via Ovid (from 1946), EMBASE via Ovid (from 1974), LILACS (from 1982), CINAHL via EBSCO (from 1981), CENTRAL (2015, issue 10), and the Cochrane Skin Group Specialized Register. We also searched five trials registers. We hand searched the bibliographies of included and excluded studies for further references to relevant trials and we contacted principal investigators for missing data.

Data extraction

Two review authors independently extracted the information from the included RCTs, and another author checked the data extraction forms for accuracy. Discrepancies were resolved by discussion.

Outcomes

Based on the protocol of the review, two primary outcomes were identified: 1) the proportion of participants with complete cure (i.e., clinical and mycological cure); and 2) the frequency and type of adverse events. We also assessed four secondary outcomes: 1) the proportion of participants with clinical cure only; 2) measurement of recurrence of the condition after the end of the intervention period; 3) percentage of

drop-outs; and 4) the time taken to cure. We present the results of primary outcomes in this abridged version.

Two review authors independently assessed the risk of bias for each included RCT according to the methods recommended in Sections 8.9 to 8.15 of the Cochrane Handbook for Systematic Reviews of Interventions. [5] The Cochrane risk of bias domains for each RCT were rated as low risk of bias, high risk of bias, and unclear risk of bias accordingly.

We presented dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI). We presented the only continuous outcome, the time taken to cure, as the mean with standard differences. When we identified clinically similar RCTs we pooled dichotomous data into a meta-analysis using random-effects model (Mantel-Haenszel method) in Revman 5.3 software. [6] We performed subgroup analyses according to dermatophyte species variation and duration of treatment, if possible. The duration of treatment was categorized into three groups: 1) short term (closest to 2 weeks, but between 1 and 4 weeks); 2) medium term (closest to 6 weeks, but between 5 and 8 weeks); and 3) long term (closest to 12 weeks, but between 9 and 14 weeks).

RESULTS

We included a total of 25 RCTs [7-31] with 4449 participants (Fig. 1). All were parallel group studies, and ten had a multi-arm design. Sample size varied from 13 to 1549 participants. Each of the 25 studies reported the types of fungus cultured.

Trichophyton species predominated over *Microsporum* species in the included studies; *T. tonsurans* and *M. canis* caused infection in the highest proportion of participants. The overall quality of included RCTs was moderate or low and in some cases 'very low' according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. [32] Fig. 2 describes our judgements about each "risk of bias" item presented as percentages across all included studies.

The included RCTs compared different active treatments: either different drugs or different regimens of the same drug. None compared an active treatment to placebo. In total, we identified five different antifungal agents and grouped the data into 13 comparisons (Fig. 3).

Terbinafine versus griseofulvin

Pooled data of five RCTs demonstrated that there was no significant difference between terbinafine (2-4 weeks) and griseofulvin (8 weeks) to achieve complete cure of *Trichophyton* or *Microsporum* infections after a 12- to 24-week follow-up (risk ratio [RR] 1.08, 95% confidence interval (CI) 0.94 to 1.24; 477 participants; I^2=41%). [7, 14, 16, 19, 26] We performed subgroup analyses according to the species causing the infection. A meta-analysis of three RCTs revealed that terbinafine (for 4 weeks) and griseofulvin (for 8 weeks) had similar effects in terms of complete cure of *Trichophyton* infections after a 12- to 24-week follow-up (RR 1.06; 95% CI 0.98 to 1.15; 328 participants; I^2=0%). [14, 16, 19] Additionally, a small RCT found no significant difference between terbinafine (for 4 weeks) and griseofulvin (for 8 weeks) to achieve complete cure of *Microsporum*

infections after a 24-week follow-up (RR: 0.45; 95% CI 0.15 to 1.35; 21 participants). [14] Pooled data of two RCTs demonstrated no significant difference between terbinafine (6 weeks) and griseofulvin (6 weeks) for achieving complete cure of *Trichophyton* infections after a 10-week follow-up (RR 1.18; 95% CI 0.74 to 1.88; 1006 participants; I^2=85%). [10, 23] However, subgroup analysis revealed that terbinafine was better than griseofulvin in terms of complete cure of *T. tonsurans* infections (RR 1.47; 95% CI 1.22 to 1.77; 764 participants). [10, 23] In children infected with *T. violaceum*, terbinafine and griseofulvin had similar effects to achieve complete cure (RR 0.91; 95% CI 0.68 to 1.24; 242 participants). [10, 23]

These two RCTs further compared medium-term (6-8 weeks) terbinafine with griseofulvin (6-12 weeks) in children with *Microsporum* infections. [10, 23] A meta-analysis of the two studies showed that griseofulvin was better than medium-term terbinafine for achieving complete cure of *Microsporum* infections after a 10- to 16-week follow-up (RR 0.68; 95% CI 0.53 to 0.86; 334 participants; I^2=0%). In addition, one of the two RCTs also compared long-term (10-12 weeks) terbinafine with griseofulvin (for 12 weeks) for treating *Microsporum* infections. [23] It demonstrated that griseofulvin was better than long-term terbinafine in terms of complete cure after a 16-week follow-up (RR 0.51; 95% CI 0.34 to 0.76; 95 participants).

A large RCT reported that 9.2% of participants in the terbinafine group and 8.3% in the griseofulvin group experienced adverse events (RR 1.11; 95% CI 0.79 to 1.57; 1549 participants). [10] The most frequent adverse events were headache, pyrexia, cough,

nasopharyngitis and vomiting. [10] Severe adverse events were rare (0.6% in both groups; RR 0.97; 95% CI 0.24 to 3.88; 1549 participants). [10] Another RCT found more adverse events in both terbinafine and griseofulvin groups (33.8% vs. 24.3%), but no significant difference was identified between the two groups (RR 1.39; 95% CI 0.83 to 2.34; 147 participants). [14] Other RCTs reported good tolerability for both terbinafine and griseofulvin because there were no or few adverse events. [7, 9, 19, 21, 26]

Different treatment durations of terbinafine

Pooled data of four RCTs [11, 13, 18, 22] demonstrated that a 4-week duration of terbinafine was better than 1 to 2-weeks of terbinafine to achieve complete cure of *Trichophyton* and *Microsporum* infections after a 12- to 20-week follow-up (RR 0.73; 95% CI 0.62 to 0.86; 552 participants; I^2=18%). However, in another RCT [23], no significant difference was found between medium-term terbinafine (6-8 weeks) and long-term terbinafine (10-12 weeks) for complete cure of *Trichophyton* or *Microsporum* infections after a 16-week follow-up (RR 1.45; 95% CI 0.97 to 2.17; 135 participants).

Five RCTs [9, 11, 13, 17, 18] reported on adverse events. Briefly, all adverse effects (e.g., headache, nausea, urticaria, and lack of appetite) were mild and comparable between the intervention groups.

Standard dose terbinafine vs. double dose terbinafine

According to the limited evidence from a small RCT [31], a standard dose (body weight 10–20 kg, 62.5 mg; 20–40 kg, 125 mg; > 40 kg, 250 mg) of terbinafine and a double

dose of terbinafine (once daily for 1 week followed by a 3-week period without treatment, two cycles in both groups) had similar effects in terms of complete cure of *Microsporum* infections after a 20-week follow-up (RR 1.2; 95% CI 0.72 to 1.76; 42 participants). Adverse effects were not addressed.

Itraconazole versus griseofulvin

Pooled data of two small RCTs identified no significant difference between itraconazole (for 2-6 weeks) and griseofulvin (for 6 weeks) to achieve a complete cure of *Trichophyton* or *Microsporum* infections after a 12- to 14-week follow-up (RR 0.92; 95% CI 0.81 to 1.05; 134 participants; I^2=0%). [16, 24]

In these two RCTs, no adverse events were identified in the itraconazole group; five cases of nausea [16, 24] and three cases of gastric problems [16] were found in the griseofulvin group.

Itraconazole versus terbinafine

A meta-analysis of two small RCTs showed that itraconazole (2-3 weeks) and terbinafine (for 2-3 weeks) had similar effects to achieve a complete cure of *Trichophyton* infections after a 12-week follow-up (RR 0.93; 95% CI 0.72 to 1.19; 160 participants; I^2=35%). [16, 20]

One RCT reported that two participants in the itraconazole group experienced urticaria and one participant in the terbinafine group experienced fever, body aches and vertigo. [20]

Ketoconazole versus griseofulvin

One study indicated that ketoconazole (for 12 weeks) appeared to be less effective than griseofulvin (for 12 weeks) for achieving complete cure of *Trichophyton* infections at the end of 12 weeks of therapy (RR 0.76; 95% CI 0.62 to 0.94; 62 participants). [15] However, when the treatment duration was extended up to a maximum of 26 weeks for participants who had not achieved a complete cure by 12 weeks, the effect of ketoconazole and griseofulvin seemed to be similar (RR 0.95; 95% CI 0.83 to 1.07; 62 participants). Another study demonstrated that ketoconazole (12 weeks) and griseofulvin (12 weeks) achieved a similar complete cure of *Trichophyton* or Microsorum infections at the end of 12 weeks of therapy (RR 0.89; 95% CI 0.57 to 1.39; 79 participants). [29]

Four RCTs reported the adverse events regarding this comparison. Adverse events in both ketoconazole and griseofulvin groups were mild and rare. Ketoconazole use was associated with two cases of abdominal pain [30], one case of urticaria [30], one case of nausea [29]; griseofulvin in one case was associated with a two-fold increase in serum alanine aminotransferase. [25]

Fluconazole versus griseofulvin

Pooled data of three RCTs [8, 12, 16] showed that fluconazole (2-4 weeks) and griseofulvin (2-4 weeks) had similar effects in achieving complete cure of *Trichophyton* or Microsporum infections after an 8- to 12-week follow-up (RR 0.92; 95% CI 0.81 to 1.05; 615 participants; I^2=0%). One RCT [12] showed that fluconazole (6 weeks) and

griseofulvin (6 weeks) were similarly effective in achieving complete cure of *Trichophyton* infection after 12-week follow-up (RR 1.06; 95% CI 0.77 to 1.46; 361 participants). Adverse effects were not reported.

Fluconazole versus terbinafine

A small RCT [16] found no significant difference between fluconazole (2-3 weeks) and terbinafine (2-3 weeks), with respect to the outcome of complete cure of *Trichophyton* infections, at the end of 12-week follow-up (RR 0.87; 95% CI 0.75 to 1.01; 100 participants). Adverse events were not addressed.

Fluconazole versus itraconazole

The same RCT [16] also found no significant difference between fluconazole (2-3 weeks) and itraconazole (2-3 weeks) in achieving complete cure of *Trichophyton* infections at the end of 12-week follow-up (RR 1.00 95% CI 0.83 to 1.20; 100 participants). Adverse events were not reported.

Different dosages of fluconazole

A small RCT [28] compared different dosages of fluconazole (1.5 mg/kg/d, 3.0 mg/kg/d, and 6.0 mg/kg/d; each for 20 days) in 41 children infected with *Trichophyton* species. Only 27 participants completed this study and the details of drop-outs in each intervention group were unclear. We used intention-to-treat (ITT) analyses and found that higher doses appeared to result in more cures than lower doses after 4-month follow-up (17% in the 1.5mg/kg/d group, 40% in the 3.0 mg/kg/d group, and 57% in

the 6.0 mg/kg/d group); however, none of these comparisons reached statistical significance (3.0 mg/kg/d vs. 1.5 mg/kg/d: RR 2.40, 95% CI 0.59 to 9.82; 6.0 mg/kg/d vs. 1.5 mg/kg/d: RR 3.43, 95% CI 0.89 to 13.15; 6.0 mg/kg/d vs. 3.0 mg/kg/d: RR 1.43, 95% CI 0.66 to 3.08). Adverse effects were not reported.

Short-term fluconazole versus medium-term fluconazole

Based on one RCT [12], short-term fluconazole (3 weeks) and medium-term fluconazole (6 weeks) made no significant difference in terms of complete cure of *T. tonsurans* and *M. canis* infections at the end of 10-week follow-up (RR 0.88; 95% CI 0.68 to 1.14; 491 participants). Adverse effects were not reported.

DISCUSSION

Current evidence supports that both griseofulvin and terbinafine are an effective first-line choice for children with tinea capitis infected with *Trichophyton* or *Microsporum* species; however, terbinafine may be a better choice for those infected with *T. tonsurans*, while griseofulvin may be a better choice for those infected with *M. canis*. We did not find any evidence to support a difference in terms of adherence between four weeks of terbinafine versus eight weeks of griseofulvin.

Limited evidence demonstrates that terbinafine, itraconazole and fluconazole appear to have similar effects for *Trichophyton* species infections, whereas ketoconazole may be less effective. There is some evidence to suggest that fluconazole is comparable to griseofulvin, especially for *Trichophyton* species infections. The majority of the current

literature deals with griseofulvin and terbinafine and there are few large, long term well-conducted trials. Future studies should be designed with attention to the merits, optimal dosages and durations of newer antifungals (e.g., itraconazole and fluconazole) both in comparison to each other and to griseofulvin or terbinafine.

Our review found that, while not all treatments for tinea capitis are available in pediatric formulations, the adverse events of griseofulvin, terbinafine, itraconazole, fluconazole and ketoconazole for treating children with tinea capitis were mild and reversible. Adverse events were comparable between terbinafine and griseofulvin. However, readers should keep in mind that RCTs with small study populations and or relatively short duration are not optimal for studying rare or long-term adverse events. Ketoconazole has been linked to adrenal insufficiency and liver toxicity including cases of death [33-35]. Reports of such adverse effects were not identified in the studies included in our review. It is notable that oral ketoconazole has been withdrawn from use in the United Kingdom and Europe since 2013. [1] In addition, both the U.S. Food and Drug Administration (FDA) [34] and Health Canada [35] have recently issued releases describing labelling changes for oral ketoconazole, and risks of potentially fatal liver damage. The FDA guidance recommended the use of oral ketoconazole only for "serious fungal infections when no other antifungal therapies are available". [34] Similarly, Health Canada recommended oral ketoconazole only for "the treatment of serious or life-threatening fungal diseases". [35]

The clinical heterogeneity between the studies in terms of the population and type of

253 causative organism, may have contributed to observed statistical heterogeneity in
254 some of our comparisons, when we pooled the data from different studies by meta-
255 analysis. As a consequence of variation between the study populations, in individual
256 patients, the most appropriate treatment may differ from treatments identified as
257 most effective in this review. All of the included RCTs were at unclear or high risk of
258 bias and the overall quality of the body of evidence was at best moderate, and for most
259 outcomes, low quality (GRADE). [32] In the absence of further information being
260 obtainable, our assessment of risk of bias was based on the published manuscripts,
261 and the results were inevitably influenced by the reporting quality of these primary
262 studies.

263 Some questions remain about whether there are advantages to the newer and
264 relatively more expensive antifungals such as terbinafine, itraconazole, and
265 fluconazole, both in comparison to each other and to griseofulvin. Further research is
266 required regarding appropriate pediatric formulations and adherence to treatment
267 (which may be needed over several weeks) in children. Patient-reported outcomes
268 such as quality of life are important for evidence-based clinical decisions and need to
269 be addressed in future studies. Clinical studies should conform to the Consolidated
270 Standards of Reporting Trials (CONSORT) 2010 statement, to improve the reporting
271 quality. [36]

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Abbreviations

CI: confidence interval

RR: risk ratio

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376 **Figure legend**

377 Fig 1. Tinea capitis. PRISMA (Preferred Reporting Items for Systematic Reviews and

378 Meta-Analyses) diagram of study flow.

379 Fig 2. Tinea capitis. Risk of bias graph

380 Fig 3. Tinea capitis. The construction of study comparisons