Pharmacotherapy of Tinea Capitis

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Editors' Note: *This month we continue the new feature—STEPped Care: An Evidence-Based Approach to Drug Therapy. These articles are designed to provide concise answers to the drug therapy questions that family physicians encounter in their daily practice. The format of the feature will follow the mnemonic STEP: safety (an analysis of adverse effects that patients and providers care about), tolerability (pooled drop-out rates from large clinical trials), effectiveness (how well the drugs work and in what patient population[s]), and price (costs of drug, but also cost-effectiveness of therapy).*[1] *Hence, the name STEPped Care.*

Since the informatics pioneers at McMaster University introduced evidence-based medicine,[2] *Slawson and colleagues*[3,4] *have brought it to mainstream family medicine education and practice. This feature is designed to further the mission of searching for the truth in medical practice. Authors will provide information in a structured format that allows the readers to get to the meat of a therapeutic issue in a way that can help physicians (and patients) make informed decisions. The articles will discourage the use of disease-oriented evidence (DOE) to make treatment decisions. Examples of DOEs include blood pressure lowering, decreases in hemoglobin A_{1c}, and so on. We will include studies that are POEMs—patient-oriented evidence that matters (myocardial infarctions, pain, strokes, mortality, etc)—with the goal of offering our patients the most practical, appropriate, and scientifically substantiated therapies. Number needed to treat to observe benefit in a single patient will also be included as a way of defining advantages in terms that are relatively easy to understand.*[5,6]

At times this effort will be frustrating. Even as vast as the biomedical literature is, it does not always support what clinicians do. We will avoid making conclusions that are not supported by POEMs. Nevertheless, POEMs should be incorporated into clinical practice. The rest is up to the reader. Blending POEMs with rational thought, clinical experience, and importantly, patient preferences can be the essence of the art of medicine.

We hope you will find these new articles useful and easy to read. Your comments and suggestions are welcome. You may contact the editors through the editorial office of JABFP or on the Internet (http://clinic.isu.edu/drugsteps/intro.html). We hope the articles provide you with useful information that can be applied in everyday practice, and we look forward to your feedback.

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Tinea capitis, or ringworm of the scalp, is the most common dermatophyte infection in pediatric populations throughout the world.[1-4] In the United States, 3 to 8 percent of the population can be affected.[5-7] Additionally, 34 percent of household contacts of children with tinea capitis are asymptomatic carriers of the infection.[8] Tinea capitis is transmitted by humans (anthropophilic) or is acquired from animals (zoophilic). *Trichophyton tonsurans* and *Microsporum audouinii* are associated with anthropophilic infections, and *Microsporum canis* is associated with zoophilic infections.[9,10]

In the United States *T tonsurans* has replaced *M audouinii* as the most common pathogen, and it causes up to 96 percent of tinea capitis infections.[11] Generally, *Trichophyton* infections are equally distributed between boys and girls and affect far more African-Americans than whites. The infection is rare in adults and adolescents (who have reached puberty), although they can be carriers. The rarity of infection is most likely

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attributed to the fungistatic activity of short- and long-chain fatty acids found in the sebum of these individuals.[3,5,7]

Although griseofulvin is the only agent approved for the treatment of tinea capitis by the Food and Drug Administration, (FDA) a variety of other systemic and topical agents, including ketoconazole, itraconazole, fluconazole, terbinafine, corticosteroids, and selenium sulfide, are also being used. Griseofulvin is fungistatic and acts by interfering with fungal nucleic acid synthesis.[12] Ketoconazole, itraconazole, and fluconazole are all fungistatic and inhibit the biosynthesis of fungal ergosterol.[13] Terbinafine is the only systemic agent that is fungicidal at low concentrations and acts by inhibiting squalene epoxide and thus ergosterol biosynthesis.[14]

Adjunctive agents used in the treatment of tinea capitis include corticosteroids and selenium sulfide. Corticosteroids are used to alter the host immune-mediated responses in patients with complicated tinea capitis, whereas selenium sulfide is used as a topical sporicidal agent.[15]

The focus of tinea capitis literature has been largely disease oriented. Most studies have evaluated the microbiologic response to certain agents using disease-oriented evidence as surrogates. There are some studies, however, that can provide POEMs (patient-oriented evidence that matters, eg, compliance rates and clinical cure, such as hair regrowth, decreased inflammation, and relapse rates) for comparative purposes.[16-30]

Methods

MEDLINE and Metacrawler search engines encompassing January 1966 through July 1998 were used to obtain clinical trials and general information regarding the treatment of tinea capitis. Search terms included "tinea capitis," "griseofulvin," "ketoconazole," "itraconazole," "fluconazole," "terbinafine," "selenium," "corticosteroids," "antifungal," "trichophyton," and "microsporum." The searches were limited to human clinical trials, pediatric patients, and review articles published in English language journals. Randomized, controlled studies were included for review if they had POEMs (eg, decreased clinic visits, inflammation, alopecia, and recurrences).

This article will delineate the role and outline the paradigm for rational use of various antifungals used to treat tinea capitis by using the STEP approach. The STEP approach involves: **s**afety (analysis of adverse events most concerning to patients and physicians), **t**olerability (pooled dropout rates from large clinical trials), **e**ffectiveness (the efficacy of medications and what patient populations benefit most), and **p**rice (cost of drug, but also cost effectiveness of therapy).

Safety and Tolerability

Treatment of tinea capitis usually requires extended therapy with medications that can cause adverse reactions in some patients. In a 12-week randomized double-blind study, 79 patients (most were African-Americans) were given griseofulvin microsize (n - 46) or ketoconazole (n - 33).[16] Although 6 percent of patients taking griseofulvin developed mild elevations in aspartate aminotransferase, these elevations were not of clinical importance as patients continued on therapy. Two patients (6 percent) in the ketoconazole group and 3 (6.5 percent) in the griseofulvin group withdrew for unknown reasons. An additional patient on ketoconazole withdrew from the study because of nausea.

A 6-week double-blind study comparing ketoconazole (n - 24) with griseofulvin microsize (n - 23) in 47 children with dermatophyte infections found a twofold increase in serum alanine and aspartate aminotransferase concentrations after 3 weeks of treatment in 1 patient on griseofulvin; however, concentrations returned to normal in subsequent visits. No adverse events were reported in the ketoconazole group.[17]

In a double-blind, randomized study of 35 patients given ultramicronized griseofulvin (n - 17) or itraconazole (n - 18), 12 percent of patients taking griseofulvin discontinued therapy because of severe nausea, vomiting, and abdominal pain.[18] These symptoms resolved after stopping griseofulvin. Although no adverse events were noted with itraconazole, 1 patient dropped out for an unstated reason.

Although headache and gastrointestinal distress are the most commonly reported adverse effects of griseofulvin, rare cases of systemic lupus, myositis, and toxic epidermal necrolysis have been reported.[17,19] Ketoconazole has caused serious hepatotoxicity, adrenal insufficiency, myopathy, and dermatologic eruptions. Whereas the latter three adverse effects have been associated with doses used in tinea capitis, hepatotoxicity has not.[17] Nei-

ther fluconazole nor itraconazole has been associated with hepatotoxicity in pediatric patients treated for tinea capitis.[13]

A 6-week study of efficacy and safety of terbinafine 125 mg/d in 12 children found 4 patients with mild transient adverse effects including anorexia (17 percent), and mild stomach upset (17 percent).[20] A comparative duration- and weight-based study of terbinafine given for 1, 2 or 4 weeks had 20 of 161 patients experiencing adverse effects. Increased hepatic enzyme levels (40 percent) and eosinophilia (25 percent) were the most common adverse effects, followed by elevated triglyceride levels (20 percent), leukocytosis (10 percent), and headache (5 percent).[21]

The major pharmacokinetic drug interactions with the antifungal medications in the treatment of tinea capitis either involve factors affecting gastrointestinal absorption or drug metabolism. The azoles (ketoconazole, itraconazole, and fluconazole) inhibit cytochrome P-450 3A4 and 2C9, and thus impair the metabolism of drugs, leading to toxic concentrations of concurrently administered drugs in some patients. Drugs including astemizole, cisapride, midazolam, triazolam, and terfenadine are well documented to have serious interactions with the azoles, especially ketoconazole and itraconazole.[22] Griseofulvin is an enzyme inducer and thus has caused therapeutic failure with agents such as oral contraceptives. Terbinafine is extensively metabolized and can interact with other drugs; however, it has been poorly studied. Cimetidine inhibits the metabolism of terbinafine and thus increases its concentrations. Terbinafine can inhibit the metabolism of certain agents such as nortriptyline.[23] Absorption of griseofulvin, itraconazole, and ketoconazole is increased with a meal. Increased gastric pH reduces absorption of itraconazole and ketoconazole.[3] As a result, agents such as proton pump inhibitors, and H_2 antagonists should be used with caution because they increase gastric pH.

Effectiveness

Trichophyton tonsurans

Disease-oriented evidence suggests agents that concentrate in the sebum (terbinafine, itraconazole, fluconazole) are more likely to achieve higher cure rates (both clinical and microbiologic) and might require shorter duration of treatment than those concentrating in eccrine sweat (ketoconazole, griseofulvin). Although this disease-oriented evidence exists, it does not provide information about clinical cure and relapse rates.

POEMs are available in a double-blind randomized comparison of micronized griseofulvin and ketoconazole.[16] This study consisted of urban African-American children aged 2 to 16 years. Outcomes included disease-oriented evidence (fungal culture results) and POEMs (clinical signs and symptoms). Of the 79 patients who were enrolled, 46 received griseofulvin (10 - 20 mg/kg/d) and 33 received ketoconazole (3.3 - 6.6 mg/kg/d). All patients taking griseofulvin had significantly improved outcomes including hair regrowth and reductions in scaling, crusting, erythema, and inflammation. Six patients taking ketoconazole (18 percent) remained symptomatic and had positive mycologic cultures after 12 weeks of therapy, while no patients taking griseofulvin failed treatment after 12 weeks. Nevertheless, mycologic cure rates were not statistically different between the two groups ($P < 0.10$).

An 8-week study of micronized griseofulvin compared with ketoconazole in 63 children (75 percent with *T tonsurans*) with tinea capitis supported these results.[24] Most of these patients (89 percent) were African-American, female (55 percent), and had a median lesion duration of 5.7 weeks before receiving treatment. Patients were randomly assigned to receive ketoconazole 5 mg/kg/d (n - 28) or griseofulvin 15 mg/kg/d (n - 35). Treatment continued until lesions resolved and microscopic examination of the hair was negative. The median duration of treatment was 108 days in those given ketoconazole and 60 days in those given griseofulvin. Children were examined at 2-week intervals for fungal cultures, new hair growth, time to complete scalp clearing, inflammation, and scaling. POEMs included sterile cultures: 92 percent and 59 percent of patients given griseofulvin and ketoconazole, respectively, had sterile cultures at final follow-up.

Based on these data, 3 patients would need to be treated with griseofulvin to prevent one treatment failure in a ketoconazole-treated group. Also, even though mean time for beginning new hair growth was not significantly different between the groups, a significantly longer time was required for complete clearing of lesions for those patients receiving ketoconazole than those on griseofulvin ($P < 0.01$). Three patients (11 per-

cent) taking ketoconazole had persistent symptoms at 6 months and needed griseofulvin treatment before clinical symptoms resolved. Two patients on ketoconazole relapsed 4 weeks after completing treatment and 1 on griseofulvin relapsed 4 months after completing treatment. Whereas the data seem to suggest that griseofulvin is effective in treating tinea capitis, results of these controlled trials might be questioned by the results found in retrospective studies. Nevertheless, one must be skeptical of these studies, as many of them involved a majority of African-American male children, whose tinea capitis is known to be more difficult to treat.[25,26]

Preliminary noncomparable data suggest that terbinafine might be useful.[21,27] A randomized double-blind study of 161 patients compared various lengths of treatment of terbinafine. Oral terbinafine taken for 1, 2, or 4 weeks showed mycologic cure rates of 88 percent, 62 percent, and 100 percent, respectively, among 24 patients with *T tonsurans* (not statistically different). Mycologic and clinical cure rates were not significantly different between the groups.

A noncomparative study of terbinafine in 13 patients with tinea capitis, 7 of whom had *T tonsurans* infection, reviewed the effects of patients receiving terbinafine pulse therapy in which 1 week of taking the medication was followed by a 2-week period off the medication.[27] Pulse therapy involves the use of a medication for a specific period, then a period without medicine, followed by a period in which the medicine is again administrated. Pulse therapy can increase compliance and decrease costs and adverse effects associated with continued administration. The disadvantages of pulse therapy in tinea capitis have not been proved, but they could include decreased effectiveness compared with standard therapies. If patients did not respond to the week of pulse therapy, a second 1-week course of terbinafine followed by a 3-week off period between the second and third pulses of treatment was administered.

Doses based on weight of each child were determined as follows: greater than 40 kg, 250 mg/d; 20 to 40 kg, 125 mg/d; less than 20 kg, 62.5 mg/d. Twelve of 13 patients were clinically and mycologically cured. Patients with moderate to severe infection required three courses of pulse therapy, and those with mild infection required one to two courses. The patient acceptance of pulse therapy and compliance was presumably high, although no specific percentages were provided.

Itraconazole has also been shown to be effective in treating tinea capitis both in daily dosing and pulse dosing, although the data supporting its efficacy are not strong. To date, no randomized trials exist comparing itraconazole with other antifungal agents for treating *T tonsurans*.[25,28] Whereas some studies of itraconazole show clinical efficacy, patient response is questionable. In a study of 25 pediatric patients with confirmed tinea capitis, after 4 weeks of itraconazole, 100 mg daily, along with a shampoo containing selenium sulfide, only 10 patients were successfully cured as defined by negative cultures and clinical improvement. The other 15 children required further treatment. After 2-week evaluations for 2 months, 14 remained culture positive, and 1 was clinically worse at week 8. Although this study was small, it does suggest that more than 50 percent of patients might not respond to 100 mg of itraconazole given daily for 4 weeks.[29] Consequently, conflicting results regarding itraconazole efficacy indicate a need for further randomized controlled studies to provide sound POEMs in treating tinea capitis.

Intralesional corticosteroid injections have been used as adjunctive therapy in patients with complicated tinea capitis. POEMs for this practice, however, are not supported by randomized, controlled clinical trials.[15] A study of 30 children with complicated tinea capitis randomized each patient to receive either griseofulvin alone or griseofulvin with intralesional triamcinolone 2.5 mg. No significant differences between groups in time to negative cultures, onset of new hair growth, or time to scalp clearing were evident.

Although the treatment of tinea capitis requires systemic therapy, adjunctive topical therapy has been found to be effective in decreasing spread of infectious spores to other persons.[31,32] A variety of topical agents are currently available as adjunctive therapy; however, selenium sulfide seems to be most commonly used. Selenium sulfide is available in a 1 percent shampoo and 2.5 percent lotion. Some important evidence exists: 54 patients with *T tonsurans* receiving griseofulvin 15 mg/kg/d were randomized to receive either the 2.5 percent lotion or 1 percent selenium sulfide shampoo or a bland nonmedicated shampoo. Patients were observed at 2-week intervals until they were clinically and mycologically cured. The selenium sulfide products

Table 1. Costs Associated with Treating Tinea Capitis in a 30-kg Child.

Medication	Dosing Regimen	Average Wholesale Price ($)
Griseofulvin	15 mg/kg/d for 6 - 8 wk	169.72 - 226.30
Ketoconazole	100 - 200 mg/d for 6 wk	67.62 - 135.24
Itraconazole pulse therapy*	5 mg/kg/d for 1 - 3 wk	68.04 - 204.12
Itraconazole	100 mg/d for 4 - 6 wk	181.04 - 272.16
Fluconazole	6 mg/kg/d for 20 d	88.95
Terbinafine pulse therapy	125 mg/d for 1 - 3 wk	23.17 - 69.51
Terbinafine	125 mg/d for 4 - 6 wk	92.68 - 139.02
Prednisone 10 mg	30 mg/d for 1 wk	1.97
Selenium sulfide 2.5% lotion 120 mL.	Applied 3 times a wk	4.07
Selenium sulfide 1% shampoo 210 mL	Applied 3 times a wk	4.57

From *Drug Topics Red Book 1998.*[34]
*Pulse therapy involves medication use for specific period (ie, 2 weeks) followed by no therapy for 1 week of no therapy, then another week of medication use.

were statistically superior to the nonmedicated shampoo for time required to eliminate shedding and viable spores. When the two different selenium products were compared, however, no difference was noted.

Microsporum (canis or audouinii)

Although *Microsporum* species are not prominent in the United States, they still cause tinea capitis in some patients. Two studies with POEMs were available. A double-blind randomized study compared itraconazole 100 mg (n - 17) with griseofulvin 500 mg (n - 17) in pediatric patients aged 2 to 11 years. Clinical and mycologic examinations were performed during treatment at 0, 2, 4 and 6 weeks and 2, 4, and 8 weeks after completing treatment. Clinical evaluation included degrees of scaling, erythema, and inflammation. In each group of patients, 15 (88 percent) were clinically cured at the 8-week posttreatment evaluation. Both patient groups had 10 percent, 40 percent, and 60 percent reductions in clinical symptoms at 2, 4 and 6 weeks of treatment, respectively.[18]

Although terbinafine therapy has resulted in important POEMs in efficacy against *T tonsurans*, only disease-oriented evidence is available, and data are not so compelling with *Microsporum* species. A study of 22 children with dry noninflammatory tinea capitis (aged 2 to 9 years, race unspecified) given terbinafine once daily for 6 weeks (doses based on weight: 62.5 mg/d if less than 20 kg, 125 mg/d if 20 to 40 kg, 250 mg/d if more than 40 kg) evaluated mycologic cure rates.[33] At the end of treatment, none of the 22 patients had complete mycologic cure. Complete mycologic cure did occur in 9 of 22 patients and 16 of 22 patients at the 4- and 8-week posttreatment evaluations, respectively. No POEM literature was found for ketoconazole, fluconazole, or selenium sulfide with regard to *Microsporum* species.

Price

The average wholesale price of each antifungal regimen as supported by both disease-oriented evidence and POEMs of cure is displayed in Table 1.[34] These costs are based on the treatment of a 30-kg child with tinea capitis. Although no pharmacoeconomic studies have been conducted comparing various agents used to treat tinea capitis, it is apparent that griseofulvin would be the most costly agent supported by POEMs for treating tinea capitis. Although ketoconazole is less expensive than griseofulvin, it might also cause more adverse effects. Other agents listed in Table 1, including itraconazole and terbinafine, do not have strong comparative POEMs to support their use; however, they could be less costly than griseofulvin. Finally, it should be noted that costs of treatment failures, transportation for clinic visits, lost wages, monitoring laboratory data, and managing adverse drug reactions are not included in Table 1.

Summary

An overview of STEPped care is presented in Table 2. Current literature suggests that griseofulvin continues to be effective in most patients with tinea capitis. Ketoconazole is no more effective than griseofulvin and causes more adverse events

Table 2. Drug STEPs Overview.

Safety and tolerability	Mild adverse effects are associated with griseofulvin, ketoconazole, terbinafine and itraconazole. While ketoconazole is associated with adrenal insufficiency, myopathy and urticaria in adults with treat tinea capitis, none of these adverse events were noted in the pediatric studies. Although clinically significant drug interactions are common with ketoconazole and itraconazole, their prevalence was not apparent in the pediatric studies
Effectiveness	Griseofulvin continues to be effective as a first-line drug in many patients. Terbinafine and itraconazole may be used in unresponsive cases. Terbinafine and itraconazole are effective in pulse and traditional doses; however, strong comparative clinical trial data supporting their use are scarce
Price	Griseofulvin is the most costly agent supported by POEM for treating tinea capitis. Other antifungal agents are less costly; however, strong clinical data are lacking to support their use
Summary	Griseofulvin continues to be the agent of choice. Randomized controlled trials need to be done to determine the role of other antifungal agents

and drug interactions. No POEMs exist for fluconazole. Itraconazole and terbinafine are promising agents. Randomized comparative studies with griseofulvin and other antifungal agents are required to clarify their role in treating tinea capitis caused by *T tonsurans* infection. Finally, adjunctive 1 percent selenium sulfide therapy is as effective as 2.5 percent selenium sulfide lotion when used in combination with systemic antifungal agents.

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