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Antifungal agents for common paediatric infections

The most common fungal infections in infants and children are mucocutaneous candidiasis, pityriasis versicolor, tinea corporis, tinea pedis and tinea capitis (1). The objective of the present update is to inform clinicians on options for treatment of these symptomatic fungal infections, due to a variety of over-the-counter (Table 1) and prescription (Table 2) drugs available. It replaces the previous position statement published in 2000 (2).

MUCOCUTANEOUS CANDIDIASIS

Candida albicans colonization can occur as early as the first week of life. Symptomatic infections such as thrush and *Candida* diaper dermatitis (CDD) may develop at any age thereafter, particularly following broad-spectrum antibiotic treatment. Systemic candidiasis is rare, but is a particular risk for premature infants (3,4).

Although mucocutaneous candidiasis is common, only a few high-quality randomized control studies of drug therapy have been published. In fact, one recent review (5) of oral candidiasis in patients with cancer found only eight studies that met the inclusion criteria. Control trials for diaper dermatitis are also rare, making it difficult to derive recommendations for optimal therapy.

Oropharyngeal candidiasis (thrush)

Oropharyngeal candidiasis (thrush) may start as early as seven days after birth, with an incidence in infants of 5% to 10% depending on the population studied (6-7). Response to antifungal agents is usually good in neonates with no major underlying condition, but a prolonged course may be required and recurrences are common. Use of an infant soother increases the incidence of thrush and may make treatment less effective, unless the soother is carefully washed after use (8).

Topical gentian violet, the oldest therapeutic agent, is moderately effective against thrush but prolonged use can cause irritation and even ulceration (9). Gentian violet stains tissue and clothing and, thus, is not well accepted by parents; it also interferes with clinical assessment.

Nystatin suspension has been used since the 1950s (10). It is well tolerated and remains the most frequently prescribed agent for thrush. The usual dosage of 200,000 units four times daily is highly effective, curing 50% of newborns after one week and 80% of newborns after two weeks of treatment (11). It should be administered after feeds.

First-generation imidazoles, such as miconazole and clotrimazole, are more effective than nystatin (12). However, miconazole gel and oral preparation of clotrimazole are not licensed in Canada. Chronic oral candidiasis can respond to clotrimazole troches (13). There is also anecdotal experience that clotrimazole suppositories in a pacifier or clotrimazole vaginal cream applied to the oral mucosa after feedings are effective against thrush (14,15). Because these therapeutic approaches have not been evaluated in controlled trials, they are not recommended as first-line therapies.

Second-generation imidazoles, such as fluconazole and itraconazole or other new oral antifungals, may be considered if conventional topical treatments fail, particularly among immunocompromised patients. Although these drugs are effective, they are not recommended as first-line management of thrush in normal children because of limited paediatric data, potentially significant adverse effects and high costs.

CDD

CDD is common during the second to fourth months of life in healthy infants (7,8). *Candida albicans* is present in the feces of 90% of such infants (13,16). Treatment should include decreasing maceration of the skin by eliminating impervious diaper covers, changing diapers frequently and leaving diapers off for long periods of time. Topical antifungal therapy is also necessary. In one randomized, double-blind, controlled trial (17) comparing miconazole ointment with zinc oxide petroleum base, miconazole was safe and more effective, particularly in moderate to severe cases. Ointments, creams and powders of nystatin, miconazole and clotrimazole are available (Table 1). It is still not clear whether concomitant oral and topical antifungals should be recommended. In two studies (18,19), no difference in the initial clinical responses was found. In another study (18), relapses were decreased (although not significantly) when an oral supplement of nonabsorbable nystatin was added to the topical ointment of nystatin (16% versus 33%).

There are no well-designed trials to assess the efficacy of adding a topical anti-inflammatory agent in treatment of CDD. Potent anti-inflammatory preparations, such as those with high concentrations of steroids, may impair the response to antifungal agents and should be avoided. The place for low concentrations of steroids (eg, 1% hydrocortisone) is unclear. Although some experts never use steroids with antifungal agents, others advocate them in CDD.

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TABLE 1
Selected topical antifungal agents for children

Antifungal agents	Cost
Nystatin cream, ointment or powder: Over-the-counter (OTC) preparations include Candistatin [*] , Mycostatin [†] and ratio-Nystatin [‡]	\$
Oral suspension (100,000 U/mL): 100,000 U to 200,000 U three to four times daily for thrush	\$\$
Clotrimazole: OTC – Canesten [§] , Clotrimaderm [¶] 1% two times daily for seven days (maximum 14 days)	\$\$
Ketoconazole cream: Nizoral ^{**} cream 2% once daily	\$\$
Ketoconazole shampoo: OTC – Nizoral ^{††} shampoo 2% once daily	\$\$
Miconazole cream or ointment: OTC – Micatin ^{††} , Micozole [¶] , Monistat ^{**} 2% one to two times daily	\$\$
Terbinafine cream: Lamisil ^{‡‡} 1% one to two times daily	\$\$\$
Gentian violet liquid: OTC 1% to 2% twice daily	\$
Selenium sulfide: OTC – Versel ^{§§} lotion 2.5%, Selsun ^{¶¶} shampoo 1% Daily	\$\$

The relative cost per 30 g treatment is indicated. Approximate relative cost for 30 g treatment includes the prescription fee (if applicable) and is based on data from 2007. Major variation in the price of products and prescription fees occur among provinces and stores. Relative price has been indicated as follows: \$ less than \$10, \$\$ from \$10 to \$25, \$\$\$ from \$25 to \$50. ^{*}Bristol-Myers Squibb Canada; [†]ConvaTec (Canada); [‡]ratio Pharm Inc, Canada; [§]Bayer AG, Germany; [¶]Taro Pharmaceuticals Inc, Canada; ^{**}McNeil Consumer Healthcare, Canada (prescription for Nizoral cream); ^{††}Johnson & Johnson Inc, Canada; ^{‡‡}Novartis AG, Switzerland; ^{§§}Valeo Pharma Inc, Canada; ^{¶¶}Chattem Inc, Canada

**PITYRIASIS VERSICOLOR
(TINEA VERSICOLOR)**

Pityriasis versicolor is a mild or chronic condition characterized by scaly hypo- or hyperpigmented lesions on the trunk. Infection often occurs in adolescents when the sebaceous glands are active. *Malassezia*, an organism restricted to invading the stratum corneum (20), causes the infection (21). Antifungal preparations can be effective, but recurrences are common (22).

Topical ketoconazole, selenium sulfide and clotrimazole are the most common treatments (23). Treatment usually consists of applying shampoo preparations, such as ketoconazole 2% or selenium sulfide as a 2.5% lotion or 1% shampoo, to the affected area for 15 min to 30 min nightly for one to two weeks, and then once a month for three months to avoid recurrences (24). In one randomized trial (25) using ketoconazole shampoo for three days or one day compared with placebo, the response was 73%, 69% and 5%, respectively.

TINEA CORPORIS

Tinea corporis (ringworm) is a superficial infection of the skin that is not covered by hair. It can occur at any age. Lesions are circular (thus the name ringworm). Common causes in Canada include *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Microsporum* species (especially *Microsporum canis* and *Epidermophyton floccosum*). These are

TABLE 2
Oral absorbable antifungal agents for common fungal infections in children

Antifungal agents	Cost
Ketoconazole 5 mg/kg/day to 10 mg/kg/day (100 mg to 200 mg daily)	\$\$\$
Fluconazole 3 mg/kg/day to 5 mg/kg/day once daily	
Using 100 mg tablets	\$\$\$\$
Using 10 mg liquid	\$\$\$\$\$
Itraconazole 5 mg/kg/day (maximum dose 400 mg daily)	
Using 100 mg capsules	\$\$\$\$
Using 10 mg/mL liquid	\$\$\$\$\$
Terbinafine	
For a child under 20 kg: 62.5 mg/day taken once daily	\$\$\$
For a child 20 kg to 40 kg: 125 mg/day taken once daily	\$\$\$
For a child over 40 kg: 250 mg/day taken once daily	\$\$\$\$

Azoles (ketoconazole, fluconazole and itraconazole) may interfere with metabolism of other drugs (see drug interaction). Prescription is required for all mentioned agents. Approximate relative cost includes the prescription fee and is based on data from 2007. Major variation in the price of products and prescription fees occur among provinces and stores. Relative price has been indicated as follows: \$\$\$ from \$25 to \$50, \$\$\$\$ from \$50 to \$100, \$\$\$\$\$ more than \$100. Cost estimate is based on treating a 20 kg child for two weeks

transmitted by direct contact with infected humans, animals (usually dogs and cats) or rarely by fomites (26). There is little difference in efficacy among clotrimazole, ketoconazole, miconazole or terbinafine. A good response usually occurs when any of these agents are applied once or twice daily for 14 to 21 days. Topical agents mixed with corticosteroids should be avoided (24).

TINEA PEDIS

Tinea pedis (athlete's foot) is a common superficial fungal infection of the foot. Causes include *T rubrum*, *T mentagrophytes* and *E floccosum*. Although tinea pedis often spreads among household members, it is uncommon in young children (26,27).

Many topical antifungals are effective against tinea pedis. Drying agents, such as Burow's solution, may be a useful adjunct for macerated or vesicular lesions. Recurrence of the infection can be prevented with good foot hygiene. Oral antifungals are indicated for infections involving the toenails. Clinical studies in children are limited, but suggest that fluconazole, itraconazole and terbinafine are effective (28,29).

TINEA CAPITIS AND SEBORRHEIC DERMATITIS

Tinea capitis (fungal infection of the scalp) is the most common paediatric superficial dermatophyte infection. The causative species vary geographically; *M canis* predominates in Europe, whereas *Trichophyton tonsurans* predominates in North America. Because tinea capitis does not respond well to topical therapy alone, oral therapy is required (Table 2) (26).

Seborrheic dermatitis and pityriasis capitis (cradle cap) are common, but usually mild, scalp infections caused by *Malassezia* species (eg, *Malassezia furfur*). The condition

often resolves with mild soap application. Shampoos containing selenium sulfide or an azole are useful in severe forms.

ORAL ANTIFUNGAL AGENTS ABSORBED SYSTEMICALLY

Fluconazole

Fluconazole is a triazole with activity against *Candida* species, some dermatophytes and many systemic mycoses. The drug is hydrophilic and, thus, present mainly in bodily fluids rather than in keratin or lipids (30). It is, therefore, not useful for routine treatment of most superficial fungal infections (31,32).

Griseofulvin

Griseofulvin is no longer available in Canada.

Itraconazole

Itraconazole is an azole with activity against many dermatophytes, *Candida* species, *M furfur* and some moulds. It has a long half-life in the skin and nails, an affinity for both lipids and keratin, and reaches the skin primarily through sebum. The drug may be excreted in sebum for one month after therapy has been discontinued. Itraconazole is available in tablet and liquid formats. Clinical trials and case series using itraconazole to treat tinea capitis have shown it to be effective (approximately 90% of the time) for infections caused by either *Trichophyton* and *Microsporum* species (33-37). Few side effects were seen in most studies using 3 mg/kg/day to 5 mg/kg/day for four to six weeks. Although more studies on safety are needed, itraconazole may become a good first-line agent for tinea capitis.

Ketoconazole

Ketoconazole was the first azole evaluated for efficacy in the treatment of resistant superficial fungal infections such as tinea capitis. Ketoconazole was found to be equivalent to griseofulvin for such cases in these clinical trials (38-41).

Terbinafine

Terbinafine is a lipophilic and keratinophilic fungicidal agent, active in vitro against dermatophytes and some moulds. It diffuses to keratinocytes from the blood stream to reach the stratum corneum and hair follicles (42). Because it is not metabolized through cytochrome P-450, many of the drug interactions seen with the azoles do not occur. Terbinafine is well tolerated, with gastrointestinal and skin reactions in only 2% to 7% of patients. Loss of the sense of taste has been reported, but resolves after therapy has ended.

Oral terbinafine is effective in the treatment of relatively resistant superficial dermatophyte infections including tinea unguium (onychomycosis), tinea pedis and tinea corporis or tinea cruris, achieving mycological cure in over 80% of adult patients (43). It is effective for children with tinea capitis at a dose of 62.5 mg/day to 250 mg/day for four weeks (44-48). Topical terbinafine 1% formulations have been effective when applied once or twice daily for two weeks. Gupta et al (49) concluded that terbinafine may

be the drug of choice for superficial fungal infections in children. Terbinafine is available in Canada as a topical 1% cream and orally as a 250 mg tablet. No liquid formulation is available.

Drug interactions

The extent to which an antifungal agent interacts with the hepatic P-450 enzyme system has implications on its potential to cause significant drug interactions (50). Azoles are metabolized by cytochrome P-450 3A (CYP 3A) and may inhibit the elimination of other drugs metabolized by this enzyme such as antiarrhythmics, cortisol, cyclosporin, estradiol and tacrolimus. Terbinafine is not an azole; it does not affect CYP 3A and it has few drug interactions.

For further details on the use of antifungal agents for common paediatric infections, the reader is referred to recent review articles (1,49,51).

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed.

Variations, taking into account individual circumstances, may be appropriate. This article also appears in the January/February 2008 issue of *The Canadian Journal of Infectious Diseases & Medical Microbiology*.