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► To cite this version:

A Maruani, S Barbarot, J.P. Gangneux, M Caseris, C Moreau, et al.. Management of tinea capitis in children following the withdrawal of griseofulvin from the French market: A fast-track algorithm proposed by the Center of Evidence of the French Society of Dermatology. *Annales de Dermatologie et de Vénérologie*, In press, 10.1016/j.annder.2022.07.001 . hal-03837146

HAL Id: hal-03837146

<https://hal.science/hal-03837146v1>

Submitted on 4 Nov 2022

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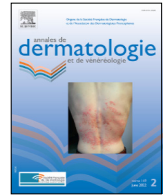


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Perspective-opinion

Management of *tinea capitis* in children following the withdrawal of griseofulvin from the French market: A fast-track algorithm proposed by the Center of Evidence of the French Society of Dermatology

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ARTICLE INFO

Article history:

Received 15 November 2021

Accepted 12 July 2022

Available online xxx

Keywords:

Dermatophytes

Tinea capitis

Children

Treatment

Griseofulvin

Terbinafine

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<https://doi.org/10.1016/j.annder.2022.07.001>

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Please cite this article as: A. Maruani, S. Barbarot, J.P. Gangneux et al., Management of *tinea capitis* in children following the withdrawal of griseofulvin from the French market: A fast-track algorithm proposed by the Center of Evidence of the French Society of Dermatology, *Annales de Dermatologie et de Vénérologie*, <https://doi.org/10.1016/j.annder.2022.07.001>

1. Introduction

Tinea capitis is a common contagious dermatophyte infection of the scalp and hair predominantly seen in children. Although the diagnosis may be strongly suspected on physical examination, microscopic morphological examination and culture or molecular biology are recommended wherever possible to identify the species of dermatophyte involved and thus ensure the most suitable therapeutic choice. The prevalence of the causative fungi varies by geographic location throughout the world [1,2]. In Europe, *tinea capitis* is now mainly caused by anthropophilic *Trichophyton* species (*T. soudanense*, *T. tonsurans*) and less often by *Microsporum* species (*M. canis*, zoophilic; *M. audouinii*, anthropophilic) [3,4].

Treatment of *tinea capitis* consists of systemic antifungals and adjuvant topical antifungals. Indeed, topical drugs are not sufficient to cure the disease and prevent spreading [5].

Griseofulvin, a fungistatic drug, is the only systemic treatment with marketing authorization in France for pediatric *tinea capitis*. In September 2007, terbinafine hydrochloride (Lamisil® Oral Granules) was approved by the US Food and Drug Administration as an alternative to griseofulvin in this indication in children from the age of 4 years [6].

In early 2021, griseofulvin was withdrawn from the market in France. At that time the French national medicines agency (Agence Nationale de Sécurité des Médicaments -ANSM-) asked French medical societies involved in the management of pediatric *tinea capitis* to examine the currently available therapeutic options for children and to propose alternative options without delay. The purpose of this paper is to provide the French algorithm proposal for alternatives, based on expert consensus.

A multidisciplinary panel of French experts, coordinated by the Centre of Evidence of the French Society of Dermatology, met 5 times between April 23, 2021 and June 6, 2021. The panel consisted of members of the French Society of Dermatology (SFD), the French Society of Medical Mycology, the French Society of Pediatric Dermatology, the French Society of Pediatrics, the Society for Infectious Pathology of French Language, and the French Society of Pharmacology and Therapeutics. The experts decided to create an

easy-to-use tool (i.e., a “management” algorithm), available within 2 months for all physicians, based on the current state of knowledge about the fungi responsible for *tinea capitis*, a non-systematic review of the literature, previous European guidelines, and their own expert report [1–5,7–11]. The algorithm and the supplemental information were approved by the ANSM in July 9, 2021 (<https://ansm.sante.fr/actualites/traitement-de-la-teigne-de-lenfant-et-indisponibilite-de-la-griseofulvine-lansm-precise-la-conduite-a-tenir>), and are available at: <https://centredepreuves.sfdermato.org/#hot-topics-english-translation>.

The main points set out in the recommendations are as follows:

- i) High recommendation concerning taking of hair sample and skin scrapings for microscopic examination and culture in the case of clinical suspicion of *tinea capitis*. The aim is to identify the dermatophyte species in the event of further treatment failure, and to better target antifungal treatment if necessary.
- ii) Probabilistic treatment: terbinafine is preferred for *tinea capitis* caused by *Trichophyton* spp. and itraconazole for *Microsporum* spp. infection. Thus for children weighing ≥ 10 kg, oral terbinafine (once a day taken during a meal) for 4 weeks should be the first-line probabilistic treatment because *Trichophyton* species are the most prevalent, with adaptation of the dose regimen to the child's weight (10 to 20 kg: 62.5 mg/d; 21 to 40 kg: 125 mg/d; > 40 kg: 250 mg/d).
- iii) Appropriate treatment based on microscopic examination: if a *Microsporum* sp. is identified, we recommend switching terbinafine to oral itraconazole (once a day outside meal-times) for 6 weeks (10 to 20 kg: 50 mg/d; > 20 kg: 100 mg/d). If *Trichophyton* sp. infection is confirmed, we recommend maintaining terbinafine.
- iv) The evidence is unclear regarding routine liver monitoring (gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase) prior to terbinafine or itraconazole treatment and 2 to 4 weeks after [8,10–12]. We recommend case-by-case decisions on such monitoring and

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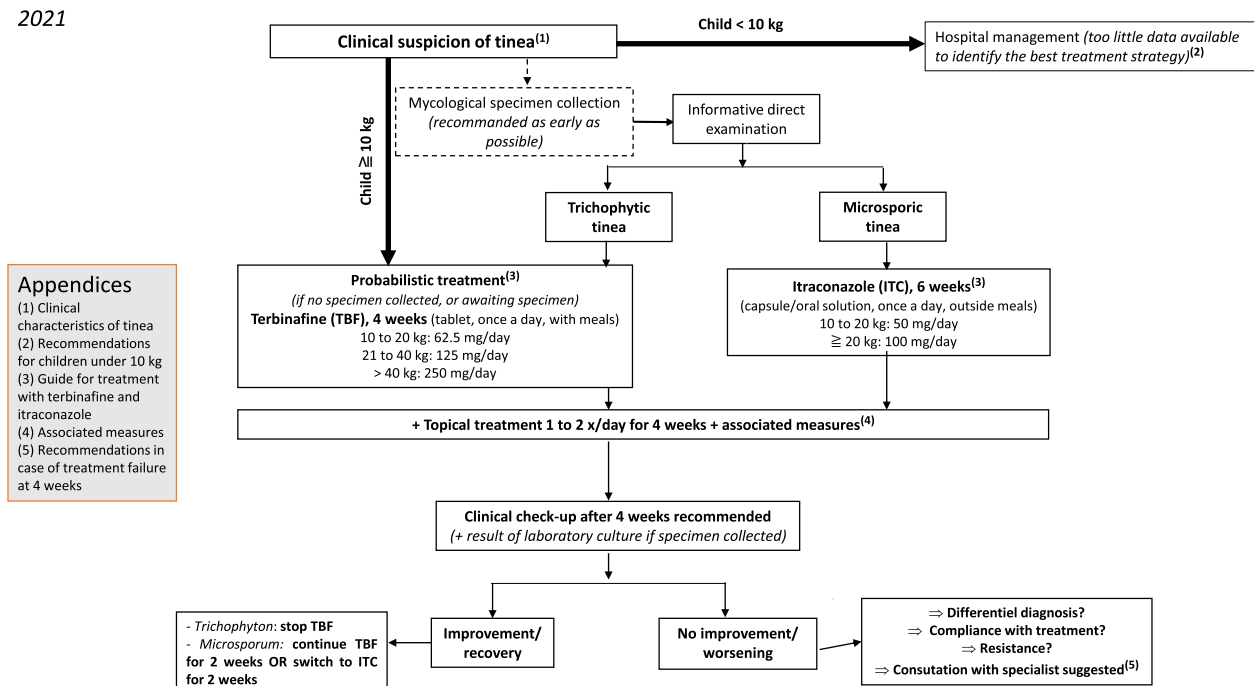


Fig. 1. Algorithm for management of *tinea capitis* in children following withdrawal of the MA for griseofulvin.

performance of lab monitoring in the case of risk factors for impaired liver function. In all cases, parents and children should be advised to discontinue treatment and consult a physician as soon as possible in the event of symptoms of acute liver damage (i.e., gastrointestinal symptoms, jaundice, asthenia, fever, rash, etc.)

- v) Topical antifungal drugs and additional measures (e.g. screening of parents, siblings and animals; washing at 60 °C of all towels, bedding etc., coming in contact with the child's head, etc.) are recommended in addition to systemic treatment.
- vi) Systematic clinical control is recommended after 4 weeks of treatment to assess treatment efficacy and correlate it with culture results. Clinical examination may reveal the following 5 possible situations, with potential solutions given:
 - 1) Completely healing of *tinea capitis*, leading to treatment withdrawal, unless *Microsporum sp.* is evidenced on culture, in which case treatment should be maintained for a further 2 weeks.
 - 2) Alleviation of *tinea capitis* but without complete resolution with evidence of *Trichophyton sp.* on culture, in which case terbinafine should be maintained for a further 2 weeks.
 - 3) Alleviation of *tinea capitis* but without complete resolution, with evidence of *Microsporum sp.*; in this case, terbinafine may be maintained for a further 2 weeks or switched to itraconazole for a further 2 weeks.
 - 4) No alleviation of *tinea capitis* or even worsening, with fungal culture showing positivity for *Microsporum sp.*; terbinafine should be switched to itraconazole for a complete 6-week course of treatment.
 - 5) No clinical improvement (or even worsening), and initial samples either not taken or negative: in the absence of therapeutic non-compliance, the child should be referred to a tertiary medical center to reassess the diagnosis and take samples for testing of antifungal drug resistance [13].
- vii) Infants <10 kg with *tinea capitis* should be referred to a tertiary medical center because of the lack of sufficient data on which to base recommendations [14,15]. Indeed pharmacokinetic and safety data are lacking in infants; terbinafine is not FDA-approved for infants, cutting the tablets into quarters is not optimal, and, although technically possible, reconstitution of the medication as an oral solution is not widespread; data regarding itraconazole at this age are scant, and an oral suspension of fluconazole may be used in newborns but is not indicated for *tinea capitis* due to inconstant efficacy [16]; topical drugs are usually not sufficiently efficacious, except for very limited fungal infections. Thus except for infections in a very limited area, treatment of *tinea capitis* in infants may include terbinafine 5 mg/kg/d, itraconazole 3–5 mg/kg/d or fluconazole 6–8 mg/kg/d for 4–6 weeks, with regular follow-up and lab monitoring.

In conclusion, the Center of Evidence of the SFD, in consultation with scientific societies, coordinated fast-track recommendations to deal with a public health situation of concern and rapidly provide therapeutic alternatives to the discontinued agent griseofulvin for *tinea capitis* in France. Because griseofulvin is becoming less and less readily available in countries throughout Europe, these recommendations may be useful beyond France. They are in line with previous British and German guidelines but are different in their presentation, since we created a pragmatic easy-to-use

algorithm (Fig. 1) [10,11]. Although the gold standard for guideline development is based on systematic reviews and meta-analyses of the literature, this is a long process that does not enable the rapid provision of answers. In addition, we were limited by the paucity of drug studies in children, especially in infants. This new situation highlights the value of creating registers to collect data for infants <10 kg presenting *tinea capitis* or for special cases such as resistance to antifungal drugs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the other members of the Center of Evidence of the French Society of Dermatology, including: Antoine Bertolotti, Guillaume Chaby, Florence Corgibet, Laurence Fardet, Nicole Jouan, Denis Jullien, Sophie Leducq, Eve Pépin, Florence Poizeau, Jean-François Sei, and Delphine Staumont. We would also like to thank Mr Laurent Elgard for managing the website of the Center of Evidence of the SFD.

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