Management of Scabies

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ABSTRACT

Scabies is a common contagious parasitic dermatosis. Transmission of the mite Sarcoptes scabiei var hominis generally occurs by skin-to-skin contact, but with crusted scabies it may also occur through fomites, such as infected clothing or bedding. Diagnosis is usually clinical. A 2010 updated Cochrane review concluded that management of scabies is based on topical scabicides, mainly 5% permethrin. However, oral ivermectin, although not licensed in many countries, may be useful, particularly for patients who cannot tolerate or comply with topical therapy and in institutional scabies epidemics. Patients should also receive detailed information about the infestation to limit further spreading. Cases resulting from close physical or sexual contact, even without symptoms, should be systematically treated. Hygienic measures should be taken after treatment is completed. Patients should be followed to confirm cure, including resolution of itching, which may take up to 4 weeks or longer.

Key Words: benzyl benzoate, ivermectin, permethrin, scabicides, scabies

Scabies is a common parasitic infection caused by the mite Sarcoptes scabiei var hominis, arthropod of the order Acarina. The worldwide prevalence has been estimated at about 300 million cases annually, although this may be an overestimate. In general, transmission occurs by direct skin-to-skin contact. In crusted scabies, transmission may also occur through infected clothing or bedding. Skin eruption with classical scabies is attributable to both the infestation and a hypersensitivity reaction to the mite. Moreover, because the eruption is usually itchy, prurigo and superinfection are common.

The main symptom is pruritus that typically worsens at night, and it is often associated with itching experienced by other family members in the household or amongst people in close physical contact with an infested individual. The lesions are commonly located in the finger webs, on the flexor surfaces of the wrists, on the elbows, in the axillae, and on the buttocks and genitalia. The elementary lesions are papules, burrows, and nodules. In crusted scabies, clinical signs include hyperkeratotic plaques, papules and nodules, particularly on the palms of the hands and the soles of the feet, although areas such as the axillae, buttocks, scalp, and genitalia in men, and breasts in women may also be affected.

The definitive diagnosis relies on the identification of mites. Multiple superficial skin samples should be obtained from characteristic lesions by scraping with a scalpel. The specimens are examined under a microscope, looking for mites, eggs, empty eggs, and scybala. Failure to find a mite is common and does not rule out scabies. New methods such as dermoscopy or adhesive tape test may increase the sensitivity of skin scraping tests and limit false-negative results. However, comparing the accuracy of different tests for diagnosing scabies remains elusive without a criterion standard. Scabies may be endemic in indigenous communities with a high rate of superinfection, which implies the need for specific management. Here, we describe the management of scabies in Western countries.
**Indication for Therapy**

People with scabies and their close physical contacts, even without symptoms, should receive treatment at the same time. Prescriptions must be provided for all household members and sexual partners.

**Patient Education**

Patients should receive detailed verbal and written information about scabies infestation. Infested individuals should be advised to avoid close physical contact until they and their sexual partners have completed treatment.

**Treatment Options**

Topical and oral products are available, although rigorous studies to guide their use are lacking. Whether oral or topical treatment is more advantageous for improved efficacy, tolerance or convenience remains unknown. Table 1 summarizes the doses and side effects of common agents used in scabies management. Topical treatment includes permethrin, lindane, benzyl benzoate, esdépallétrine (bioallethrin), crotamiton, and precipitated sulfur. Topical scabicides have neurotoxic effects on mites and larvae. Despite the varied methodological quality of trials, a recent meta-analysis suggested that topical permethrin is the most effective. Oral ivermectin interrupts the gamma-aminobutyric acid-induced neurotransmission of many parasites (including mites). However, oral ivermectin is not licensed in most countries. It must be given at 200 µg/kg as a single dose in patients >2 years of age and >15 kg. A second dose is necessary 2 weeks later due to the lack of ovicidal action of the drug. Because ingestion of food increases the bioavailability of ivermectin by a factor of 2, taking it with food might enhance the penetration of the drug into the epidermis. Finally, topical permethrin is reasonable as first-line therapy. If permethrin is not available (e.g., in France), benzyl benzoate may be used. Oral ivermectin is a good but more expensive alternative; however, this agent may be preferred for patients who cannot tolerate topical therapy or are unlikely to adhere to such a therapeutic regimen. In classical scabies, the combination of topical therapy and oral ivermectin has never been compared with either treatment alone. Table 2 presents strategies of treatment according to the clinical picture.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Treatment Regimen</th>
<th>Contraindication</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permethrin</td>
<td>5% cream</td>
<td>Rinsed off after 8-12 hrs</td>
<td>Effective, well tolerated, safe</td>
<td>Itching and stinging on application</td>
<td></td>
<td>Second application often routinely prescribed 1 week after the first application</td>
</tr>
<tr>
<td>Lindane</td>
<td>1% lotion or cream</td>
<td>Rinsed off after 6 hrs</td>
<td>Pregnant women, infants, seizure disorders</td>
<td>Effective, inexpensive</td>
<td>Cramps, dizziness, seizures in children</td>
<td>Withdrawn in the European Union because of neurotoxicity concerns</td>
</tr>
<tr>
<td>Benzyl benzoate</td>
<td>25% ointment</td>
<td>Rinsed off after 24 hrs (once or several times)</td>
<td>Pregnant women and infants (limit duration of use to 12 hrs)</td>
<td>Effective, inexpensive</td>
<td>Can cause severe skin irritation</td>
<td>Not currently available in Canada, approved in Europe</td>
</tr>
<tr>
<td>Esdépallétrine</td>
<td>0.6% aerosol</td>
<td>Rinsed off after 12 hrs</td>
<td>People with asthma</td>
<td>Well tolerated, safe for infants</td>
<td>Questionable efficacy</td>
<td>Not available in Canada, often used on scabies nodules in children</td>
</tr>
<tr>
<td>Crotamiton</td>
<td>10% ointment</td>
<td>Rinsed off after 24 hrs and then reapplied for an additional 24 hrs</td>
<td></td>
<td>Safe for infants, pregnant and</td>
<td>Questionable efficacy, skin irritation</td>
<td></td>
</tr>
<tr>
<td>Precipitated sulfur</td>
<td>2%-10% precipitate in</td>
<td>Rinsed off after 24 hrs and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scabies is considered to be a sexually transmitted disease, therefore, patients should undergo routine examination for sexually transmitted infection.\textsuperscript{12}

Patients must receive detailed information about scabies infestation and therapeutic options, including the amount of drug to be used and proper administration. Topical treatment must be applied to the entire skin surface, including the scalp, all folds, groin, navel, and external genitalia, as well as the skin under the nails. In adults with classical scabies, treating the face is controversial, but in babies, the face must be treated, because transmission may occur by breastfeeding. Hands should not be washed during therapy, otherwise the treatment should be reapplied. If the treatment is applied by someone without scabies, this person should wear medical gloves during administration.

After the completion of treatment, patients should use fresh, clean bedding and clothing. If possible, potentially contaminated clothes and bedding should be washed at high temperature (>50°C) or kept in a plastic bag for up to 72 hours, because mites that are separated from the human host will die within this time period. The use of insecticidal powder or aerosol products should be reserved for materials or objects that cannot be washed.\textsuperscript{13}

With classical scabies, the time course for the eradication of parasites after treatment is not known, but there is some concern that patients receiving oral ivermectin may remain contagious longer than those receiving topical therapies.\textsuperscript{1,10}

**Special Treatment Considerations (Table 2)**

**Impetigo**
Scabies complicated by impetigo requires combined antiseptic and antibiotic therapy against Streptococcus pyogenes and Staphylococcus aureus. Oral ivermectin is preferred if skin is damaged.

**Crusted Scabies**
Management of crusted scabies generally necessitates admission to the hospital and isolation of the patient because of the risk of transmission to people in physical contact. Active epidemiological measures to ensure treatment of all individuals in contact are necessary. Hyperkeratosis is treated with a keratolytic agent. The nails are cut short and brushed with a scabicidal agent.\textsuperscript{13} The combination of topical and oral therapy is advised,\textsuperscript{14} although evidence is lacking regarding efficacy. Topical treatment may be repeated. Dosing and frequency of administration is based on the severity of infection. The required number of doses of ivermectin remains uncertain, but depending on infection severity, 3 to 7 doses have been proposed.\textsuperscript{10} A test of cure may be performed for crusted scabies.

**Pregnancy or Breastfeeding**
Permethrin, benzyl benzoate, and sulphur appear to be safe, although evidence is limited.\textsuperscript{15} Oral ivermectin is contraindicated.

**Children**
Permethrin may be used in infants. Benzyl benzoate and esdépallétrine are safe in children <2 years of age, but duration of use should be limited to 12 hours. Ivermectin is not approved for children <15 kg.
Institutional Outbreaks

Management of institutional outbreaks has never been evaluated. The control of institutional outbreaks relies on prompt recognition of the index case, formation of an outbreak management team, determining the extent of the outbreak and risk factors for transmission, immediate implementation of infection control practices, adequate education of all involved individuals, simultaneous treatment of cases and all exposed people, and concomitant environmental disinfection.  

Clinical Conditions | Recommended Therapy | Alternative Therapy | Additional Measures | Comments |
--- | --- | --- | --- | --- |
Classical scabies | Two applications of permethrin 5% or benzyl benzoate | Two doses of oral IVERmectin, 200 µg/kg (at days 1 and 14) | | People in close physical contact, even without symptoms, should receive treatment at the same time |
Crusted scabies | Several applications of permethrin or benzyl benzoate with repeated doses of oral ivermectin | | Keratolytic agents must be used | Control the spread of scabies infection |
Children <2 years of age | Permethrin or benzyl benzoate (limit duration of use to 12 hrs) | Ivermectin is contraindicated in children <15 kg | | |
Pregnancy | Permethrin, benzyl benzoate (limit duration of use to 12 hrs), and sulfur | Ivermectin is contraindicated | | |
Superinfected scabies | Oral ivermectin is preferred if skin is affected | Antibiotherapy (antibiotics) before topical treatment | | Risk of post-streptococcal glomerulonephritis and systemic sepsis |
Institutional outbreaks | Treat clinical cases as for classical and crusted scabies | Simultaneously treat all cases and all exposed people | Formation of an outbreak management team | |

Table 2. Treatment of scabies by clinical features or situation

Follow-up

Patients should understand that after treatment is completed, itching may persist for several weeks, especially in atopic individuals. If itching continues after 4 weeks, the cause should be reinvestigated (Table 3). Symptomatic relief may be achieved with an emollient. A test of cure is not usually required with classical scabies.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Potential Causes</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous irritation</td>
<td>Overtreatment</td>
<td>Intensive use of emollient</td>
</tr>
<tr>
<td></td>
<td>Eczematization</td>
<td>Intensive use of emollient</td>
</tr>
<tr>
<td></td>
<td>Contact dermatitis</td>
<td>Topical steroid</td>
</tr>
<tr>
<td></td>
<td>Poor compliance: inappropriate or insufficient treatment</td>
<td>Further scabicide application</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>Resistance to scabicide</td>
<td>Change scabicide</td>
</tr>
<tr>
<td></td>
<td>Reinfection or relapse</td>
<td>Further scabicide application</td>
</tr>
<tr>
<td>Psychogenic pruritus</td>
<td>Delusions of parasitosis</td>
<td>Psychiatric referral</td>
</tr>
<tr>
<td></td>
<td>Nonparasitic dermatosis</td>
<td>Treat the underlying cause</td>
</tr>
</tbody>
</table>

Table 3. Causes of persistent itching after scabicide therapy and suggested management (table adapted from reference 13)
Conclusion

Scabies is a frequent, contagious dermatosis. Its management is sometimes complex and updated treatment guidelines are useful.\textsuperscript{12,17} Patients and people in close physical contact with infested individuals should receive detailed information from healthcare providers, because treatment failure is often attributable to poor compliance or incorrectly carrying out instructions of prescribed therapy. Decision-making for topical or oral treatment may vary by situation. Randomized controlled trials comparing topical treatment to oral ivermectin demonstrating a high level of evidence are needed.

References


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1. Management of Scabies
2. Silk Fabrics in the Management of Atopic Dermatitis
3. Update on Drugs and Drug News - March 2012

CUSTOM DERMATOLOGY SEARCH:Loading
ORIGINAL ARTICLE

Treatment of scabies: Comparison of permethrin 5% versus ivermectin

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ABSTRACT

Scabies is an ectoparasitic, highly contagious skin disease caused by a mite called Sarcoptes scabiei. The insecticides ivermectin and permethrin are commonly used for treatment of scabies. This study aimed at comparing the efficacy of oral ivermectin with topical permethrin in treating scabies. Two hundred and forty-two patients with scabies attending the dermatology outpatient department of Sina Hospital, Tabriz University of Medical Sciences were admitted. Patients were divided into two groups randomly. The first group and their family contacts received 5% permethrin cream and the other received oral ivermectin. Treatment was evaluated at intervals of 2 and 4 weeks. A single dose of ivermectin provided a cure rate of 85.9% at a 2-week interval, which increased to 100% after crossing over to the permethrin group at a 4-week interval. Twice application of permethrin with a 1-week interval was effective in 92.5% of patients, which increased to 94.2% after crossing over to the ivermectin group at a 4-week interval. Permethrin-treated patients recovered earlier. Twice application of permethrin with a 1-week interval is superior to a single dose of ivermectin. The temporal dissociation in clinical response suggests that ivermectin may not be effective against all the stages in the life cycle of the parasite.

Key words: contagious, oral ivermectin, permethrin 5%, scabies, skin disease.

INTRODUCTION

Scabies is a common ectoparasitic infection caused by a mite, Sarcoptes scabiei var. hominis. It causes substantial morbidity from secondary infections and post-infective complications such as acute post-streptococcal glomerulonephritis.¹ Lesions consist of tiny gray specks, burrows, or both. Non-specific lesions consist of papules and itchy excoriations and crusts. The lesions are usually found in interdigital folds of the hands, the flexor aspects of the forearms, axillary folds, nipple areola and the periumbilical area.² Disease control requires treatment of the affected individual and all people they have been in contact with, but is often hampered by inappropriate or delayed diagnosis, poor treatment compliance, and improper use of topical compounds such as benzyl benzoate.³ In addition to concerns over the toxicity of such compounds, parasite resistance seems to be increasing. Treatment of scabies in poor countries needs to integrate drug treatment programs with efforts to improve the socioeconomic conditions and education programs to reduce stigma.⁴ Treatment options that were formerly available included sulfur, crotamiton lotion and 25% benzyl benzoate. Sulfur in 5–10% petrolatum is relatively cheap, but must be applied on three successive nights to be effective. It is considered the safest treatment for pregnant women and very young children.⁵ For many years, lindane was the preferred therapy until concern was voiced about its efficacy and safety. Permethrin, malathion have become treatments of choice.⁶ Currently, 5% topical permethrin cream is considered by many as the drug of choice in the treatment of scabies.⁷ Permethrin is a synthetic pyrethroid and was one of the first thermos-stable and photostable insecticides developed following the elucidation of the chemical structures of natural pyrethrins in 1947.⁸ Permethrin demonstrates extremely low mammalian toxicity, combined with insecticidal activity even higher than natural pyrethrines. These properties, backed by extensive experience of safety over 20 years in the veterinary and agricultural industry, made this compound an ideal candidate for use as a treatment for scabies.⁹ Ivermectin is a novel antiparasitic agent effective against a variety of endoparasites and ectoparasites. With a single oral dose, ivermectin is effective against intestinal nematodes and appears to be a promising treatment for head lice infestations, which are common co-infections in developing countries.¹⁰ It is not yet approved by the US Food and Drug Administration for the treatment of human scabies.¹¹ Initial reports have highlighted the utility of oral ivermectin in the treatment of scabies. Hence, it was considered worthwhile to generate more data regarding the human use of ivermectin in the treatment of
scabies, comparing the result with the currently available first-line treatment of scabies, permethrin. In the present study, we compared the efficacy and safety of oral ivermectin with topical permethrin in the treatment of scabies.

METHODS

In this clinical trial study, 242 patients aged 2–84 years (mean 42 ± 14/36) with a diagnosis of scabies participated from April 2008 to April 2011. All of the patients younger than 2 years of age, pregnant and lactating women, patients with past history of seizures, severe systemic disorders, immunosuppression and crusted scabies (Norwegian) were excluded. Informed consents were obtained from patients. Patients had not received any topical or systemic acaricide therapy for 1 month prior to the study. The permethrin dermal cream and oral ivermectin were packaged in identical-appearing boxes, the contents of which were unknown to the evaluation team. This blinding was maintained throughout the study. Similarly, the treatment team members who applied medications took no part in pretreatment scoring of the severity and extent of the infestations and played no role in subsequent evaluations. Prior to entry into the study, patients were given a physical examination, and their history of infestations, antibiotic therapy and other pertinent information was recorded. Age, sex, height and weight were recorded for demographic comparison. The diagnosis of scabies was made by the demonstration of eggs, larve, mites or fecal material by light microscopy or by the presence of the following three criteria: demonstration of a burrow and/or typical scabetic lesions at the classical sites; nocturnal pruritus; and history of similar symptoms in their families and/or close contacts. Patients who satisfied the above criteria were divided into two groups randomly. The first group and their family contacts received 5% permethrin cream (group A) and the other received oral ivermectin (group B). The treatment with permethrin 5% consisted of two applications of the product with a 1-week interval. Patients were advised to apply the cream from head to toe on each occasion and to take a shower 12 h later. Oral ivermectin was given to group B in a single dose of 200 μg/kg bodyweight. Clinical evaluations after treatment were made by experienced investigators without knowledge of the treatments. At all evaluation times, they recorded the sites of lesions on body diagram sheets. The notations of their appearance and whether or not they were new or residuals of original lesions were determined by comparison with the pretreatment photograph. New lesions were also scraped for microscopic examination. Severity of infestation pretreatment of all patients was considered as: (i) mild (<50); (ii) moderate (50–100); and (iii) severe (>100). Patients were treated with the scabicides and then followed up at intervals of 2 and 4 weeks. Cure was defined as the absence of new lesions and all old lesions healed. Treatment failure was defined as a patient with microscopically-confirmed new lesions at 1 month and who was not considered cured at 2 weeks. The term re-infestation was applied to the patients who were completely clear at 2 weeks and developed new lesions with positive microscopic findings at 1 month. In case of treatment failure, the patient was crossed over to the other group. At the end of the fourth week, another evaluation was performed. The results of the study were statistically analyzed using SPSS ver. 16. To account for statistical differences in the two groups, a χ²-test or Fisher’s exact test was used, as appropriate. Student’s t-test was used for numerical data. P < 0.05 was considered significant.

RESULTS

A total of 272 patients were studied. Thirty-four patients (18 from group A and 12 from group B) were not able to return after the first follow-up examination and were therefore excluded from the study. The remaining 242 patients consisted of 132 males (54.5%) and 110 females (45.5%). Their ages ranged 3–78 years (mean age, 36.24 ± 12.6). Of these 242 patients, 121 were treated with permethrin 5% and the others with ivermectin. The demography of the two treatment groups showed no significant difference (Table 1). On entry into the study, the number of patients in each treatment group who were graded as having mild, moderate or severe infestations was not significantly different (Table 2). At 2 weeks post-treatment, treatment was effective in 112 (92.5%) patients in the permethrin 5% group and 104 patients (85.9%) in the ivermectin group (Table 3). This difference was not significant (P = 0.42). The 26 patients (18 male and eight female) who had not improved were crossed over to the other group. On the next follow up, at 4 weeks post-treatment, seven patients in the permethrin 5% group who showed no response at the first follow up and were subsequently treated with

Table 1. Demographic characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Permethrin 5% (n = 121)</th>
<th>Ivermectin (n = 121)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.74 ± 17.32</td>
<td>37.12 ± 13.14</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72</td>
<td>60</td>
<td>0.36</td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>64</td>
<td>0.32</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ± 32</td>
<td>178 ± 14</td>
<td>0.38</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 ± 36</td>
<td>72 ± 58</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Table 2. Severity of infestation pretreatment of all patients

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Permethrin 5% (n = 121)</th>
<th>Ivermectin (n = 121)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (&lt;50)</td>
<td>21</td>
<td>24</td>
<td>0.62</td>
</tr>
<tr>
<td>Moderate (50–100)</td>
<td>34</td>
<td>27</td>
<td>0.48</td>
</tr>
<tr>
<td>Severe (&gt;100)</td>
<td>66</td>
<td>70</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Table 3. Response to treatment after 2 weeks

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 121)</th>
<th>Group B (n = 121)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectively treated patients at week 2</td>
<td>112 (92.5)</td>
<td>104 (85.9)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Ivermectin still had severe itching. In contrast, all 17 patients not responding to ivermectin who were then treated with permethrin showed improvement in itching and skin lesions. Only nine patients (six in the permethrin group and three in the ivermectin group) experienced irritation after application of the drug, but none had allergic reactions.

**DISCUSSION**

For the past 50 years, lindane has been the preferred therapy for scabies. This product has become the most widely used antiscabietic drug in many countries, including Iran. During recent years, resistance to lindane seems to be rising and there are reports of several clusters of patients with lindane-resistant scabies worldwide. Permethrin cream (5%) was introduced in 1989 for the treatment of scabies and seems to be a good substitute for lindane. It is considered to be the drug of choice in many countries. The 5% permethrin preparation kills the organisms and eggs, and has an extremely low rate of absorption, making the toxicity potential non-existent. Resistance to permethrin in developed countries was reported in 1999. Ivermectin is a novel antiparasitic agent effective against a variety of endoparasites and ectoparasites. In this study, two applications of permethrin with a 1-week interval was as effective as a single oral dose of ivermectin by 2 weeks ($P = 42$). This study also concurs with the excellent cure rates (90–100%) observed in the initial studies with permethrin. The lack of efficacy of a single dose of ivermectin in some patients may be due to the lack of ovicidal action of ivermectin. Ivermectin, because of its specific site of action, may not be effective against the younger stages of the parasite inside the egg because the nervous system has not yet developed. The concentration achieved in the skin may also be variable because ivermectin is orally administrated. These factors could also explain the temporal delay in complete recovery observed in the ivermectin group. Because ivermectin has not been proven to be ovicidal, a single dose of 200 $\mu\text{g/kg}$ body weight may be inadequate to eradicate the different stages of the parasite, and a higher dose or a second dose may be required within 1–2 weeks for higher cure rate. In the study carried out by Usah et al., a higher number of patients showed clearance of lesions as compared to our results. This could be explained due to the longer follow up. In the study carried out by Khan et al., a 100% cure was seen in both treatment groups, possibly because the study was carried out on a smaller number of patients with follow up of 2 weeks, and because ages were 12 years or above when the activity of sebaceous glands is higher. Regarding side-effects, permethrin was found to be significantly safer than ivermectin ($P = 0.05$). Although ivermectin was as effective as permethrin, it has few outweighing advantages over topical permethrin. It is cost-effective and can be given to masses with better compliance with or without supervision. It can also be given safely to patients of scabies with secondary eczematization, erosions or ulcers where topical therapies such as permethrin, lindane and benzyl benzoate can cause serious cutaneous and systemic side-effects in addition to the problem of compliance.

**REFERENCES**

Permethrin and Ivermectin for Scabies
Bart J. Currie, F.R.A.C.P., and James S. McCarthy, F.R.A.C.P.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors’ clinical recommendations.

In a remote aboriginal community in tropical northern Australia, a mother comes to the health center with her 4-year-old son, who has multiple sores on the skin of his arms and legs. He is treated with a single dose of intramuscular penicillin G benzathine and with the application of topical 5% permethrin cream over his whole body. A week later, the pyoderma has substantially resolved, but the boy continues to scratch his hands and feet. The clinic nurse visits the family house and finds that skin sores are present on both infants who live in the household, three of the six young children, and one of the three adolescents. Some also have scratches and small interdigital excoriations, which are consistent with scabies. An infirm elderly aunt living in the house is found to have widespread areas of extensively crusted and scaly skin, which are especially prominent on her hands, elbows, armpits, knees, and buttocks. All the household members are given topical permethrin, and the aunt is referred to the hospital for oral ivermectin therapy.

The Clinical Problem
Scabies is an ectoparasitic infection caused in humans by the scabies mite Sarcoptes scabiei variety hominis. Infection occurs as a result of direct skin-to-skin contact; fomite transmission from mites attached to clothing, bedding, and towels is uncommon. Infection occurs worldwide, although estimates of 300 million cases yearly are possibly exaggerated. The infection is endemic in many impoverished communities, but prevalence rates vary widely; seasonal outbreaks and documented peaks during times of war are probably related to crowding and population movements. In some industrialized countries, scabies is endemic in economically disadvantaged populations, and outbreaks occur in nursing homes and hospitals.

The classic manifestation of scabies is generalized itching that is more intense at night and that causes discomfort to the patient; however, complications and death can also occur, usually as a result of secondary bacterial pyoderma, commonly caused by Streptococcus pyogenes or Staphylococcus aureus. Such secondary infection can lead to complications such as post-streptococcal glomerulonephritis and systemic sepsis.

Pathophysiology and Effect of Therapy
The life cycle of S. scabiei (Fig. 1) begins when adult mites burrow into the skin of the human host and mate, and the females lay eggs. Larvae hatch from the eggs and eventually develop into adult mites, thus completing the life cycle. The skin lesions of scabies are due both to the burrows of the mites and to more widespread inflamed areas.
matory responses in the skin, caused by a hypersensitivity reaction to the mites and to their saliva or excreta.\(^2,4,11\) In the vast majority of scabies infections, the number of female mites is thought to be limited to 10 to 15, and burrows may be difficult to identify.\(^4\) In this classic presentation, lesions are most often present on the interdigital finger webs and flexor surfaces of the wrists. Elbows, axillae, buttocks, and genitalia are quite frequently involved as well (Fig. 2), as are the breast areolae in women. Atypical presentations such as involvement of the scalp can occur in infants and the elderly. Nodular scabies results from an exaggerated hypersensitivity reaction and is characterized by chronic, pruritic nodules that are often localized to the axillae, groin, and genitalia, such as the scrotum.\(^2\)

Crusted scabies, formerly called Norwegian scabies, occurs when mite replication is not controlled by the host’s immune system and hyperinfection develops (Fig. 2). This form of scabies usually occurs in immunocompromised patients such as patients with human immunodeficiency virus infection or those who are receiving immunosuppressive therapy.\(^6\) Patients with crusted scabies are highly infectious, can be “core transmitters” in communities and in institutional outbreaks, have high rates of death from secondary bacterial sepsis, and are difficult to treat.\(^10\)

A variety of agents, most of them topical, have

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**Figure 1. Life Cycle of Sarcoptes scabiei.**
been used to treat scabies. These include 5 to 10% sulfur in paraffin, an agent used widely in Africa and South America; 1% lindane, which is no longer used in many Western countries because of concerns regarding neurotoxicity; 10 to 25% benzyl benzoate, which is often used in Europe and Australia; malathion; 10% crotamiton; and 5% tea-tree oil in combination with benzyl benzoate.

Permethrin is a synthetic pyrethroid agent that is applied as a topical 5% cream for the treatment of scabies. It disrupts the function of voltage-gated sodium channels of arthropods, causing prolonged depolarization of nerve-cell

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**Figure 2. Manifestations of Scabies.**

Interdigital lesions are a typical manifestation of classic scabies (Panel A). A pattern of excoriated pustules in the axilla is characteristic of scabies with secondary bacterial infection (Panel B). Crusted scabies can be manifested as excoriated, lichenified skin on the wrists and hands (Panel C). A case of severe crusted scabies can result in sloughing of layers of thick, hyperkeratotic skin, with fissures that can result in secondary bacterial infection and the potential for bacteremia and systemic sepsis (Panel D). Panel A reprinted from Chosidow.
membranes and disrupting neurotransmission.\textsuperscript{15} The selective neurotoxic effect of permethrin on invertebrates is due to structural differences in voltage-gated sodium channels between vertebrates and invertebrates.\textsuperscript{15} Permethrin 5% cream was approved for treatment of scabies by the Food and Drug Administration (FDA) in 1989.

Ivermectin is a semisynthetic macrocyclic lactone antibiotic agent that is administered orally. It disrupts the function of a class of ligand-gated chloride ion channels, causing persistent opening of the channels.\textsuperscript{16} This interaction is well studied in nematodes, with both \(\gamma\)-aminobutyric acid and glutamate-gated channels identified as targets.\textsuperscript{16} However, the target of this drug in the scabies mite has yet to be identified; only a pH-gated chloride channel that is sensitive to ivermectin has been described.\textsuperscript{17} Although the selectivity of ivermectin for invertebrates is incompletely understood, it may be explained, in part, by the theory that in vertebrates, drug pumps of the P-glycoprotein family exclude the drug from its potential site of action.\textsuperscript{16} Oral ivermectin has been approved for the treatment of scabies in France since 2001. It is not licensed for the treatment of scabies in the United States, United Kingdom, or Australia but has increasingly been used off-label in those countries.

**Clinical Evidence**

There is a paucity of high-quality studies that compare various therapies for scabies.\textsuperscript{12} An assessment of the findings of published studies is impeded by the relatively small size of the studies and the lack of standardization of diagnosis and follow-up.\textsuperscript{18} A Cochrane review concluded that there are insufficient data available to compare the relative efficacies of topical permethrin and topical benzyl benzoate.\textsuperscript{12} However, that review did show that permethrin was more effective than both crotamiton and lindane (relative risk of treatment failure with permethrin as compared with crotamiton, 0.24 in two trials involving 194 subjects, and relative risk with permethrin as compared with lindane, 0.32 in five trials involving 753 subjects).\textsuperscript{18}

The Cochrane review also concluded that oral ivermectin appeared to be more effective than both lindane and topical benzyl benzoate (relative risk of treatment failure with ivermectin as compared with lindane, 0.36 in two trials involving 193 subjects, and relative risk with ivermectin as compared with benzyl benzoate, 0.50 in three trials involving 192 subjects).\textsuperscript{12} However, a recent study showed that there was a higher rate of treatment failure with single-dose ivermectin than with topical benzyl benzoate.\textsuperscript{19} This finding may reflect the fact that ivermectin does not sterilize scabies eggs. Therefore, a second dose of ivermectin is usually administered at least 1 week after the first dose to kill the newly hatched mites. Further support for this concept comes from a trial that compared ivermectin with topical permethrin in 85 patients.\textsuperscript{20} In that trial, a single dose of ivermectin was less effective than topical permethrin (cure rate of 70% vs. 98%), but if a second dose of ivermectin was administered to patients who did not have a response after the first dose, the cure rate with ivermectin rose to 95%.

There are no comparative studies of the safety and efficacy of various therapies for scabies in special groups such as infants, small children, and the elderly or for cases of crusted scabies. However, observational studies have shown that ivermectin regimens are effective after the failure of topical therapy in patients with crusted scabies.\textsuperscript{10,21,22}

**Clinical Use**

Our recommendations for the treatment of various scabies syndromes are summarized in Table 1. For the treatment of classical scabies, permethrin 5% cream is our preferred agent. To ensure a reliable cure, the cream should be applied to the entire surface of the skin except around the eyes. Although some guidelines suggest that topical therapy need not be applied above the neck, we believe that including this area is particularly important in small children and the elderly, in whom the infection quite often involves the scalp. Particular attention should be paid to the areas that are most often involved, including the areas between the fingers and toes, under the arms, and under the fingernails and toenails; the wrists; the external genitalia; and the buttocks.\textsuperscript{23} To maximize exposure of the mites to the drug, it is generally recommended that the cream be applied in the evening and left on overnight. To eradicate any mites that were not exposed at the time of the first treatment, it is generally recommended that a second application be administered 1 to
Table 1. Therapies for Scabies.

<table>
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<tr>
<th>Purpose of Therapy</th>
<th>Recommended Therapy</th>
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<tr>
<td>Treatment for classic scabies</td>
<td>Two applications — one on day 1 and one between day 8 and day 15 — of topical permethrin 5%, applied in the evening and left on overnight</td>
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<tr>
<td>Treatment for crusted scabies</td>
<td>Both topical permethrin 5% every 2 to 3 days for 1 to 2 weeks and oral ivermectin (200 µg/kg/dose), taken with food, administered as three doses (days 1, 2, and 8), five doses (days 1, 2, 8, 9, and 15) or seven doses (days 1, 2, 8, 9, 15, 22, and 29), depending on severity of infection*</td>
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<tr>
<td>Prevention of infection in close contacts of patients with scabies</td>
<td>A single application of topical permethrin 5% applied in the evening and left on overnight</td>
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<tr>
<td>Management of institutional outbreak of scabies</td>
<td>Treat persons with clinic cases as recommended above for classic and crusted scabies and treat all potentially exposed residents, staff, and visitors as recommended above for contacts</td>
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<tr>
<td>Prevention in communities where scabies is endemic or management of community outbreak</td>
<td>Adopt multifaceted approach that includes education and community involvement; treat clinical cases as recommended above for persons with classic and crusted scabies and all family and household members as recommended above for contacts; consider treating all other community members as recommended above for contacts</td>
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<th>Alternative Therapy</th>
<th>Comments</th>
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<tr>
<td>Two doses of oral ivermectin (200 µg/kg/dose), taken with food — one on day 1 and one between day 8 and day 15*</td>
<td>Keratolytic creams should be used for skin crusts; maintain vigilance for the development of sepsis; apply appropriate measures to control the spread of scabies infection</td>
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<td>Topical benzyl benzoate 25% (with or without tea-tree oil 5%) instead of permethrin</td>
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<tr>
<td>Oral ivermectin (200 µg/kg/dose), taken with food, administered as a single dose*</td>
<td>Look for “core transmitter” index cases with crusted scabies; give attention to planning and logistics of therapy; apply appropriate measures to control the spread of scabies infection</td>
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* Ivermectin is not approved for this indication by the Food and Drug Administration; there are insufficient data on the safety of ivermectin in pregnancy and in children younger than 5 years of age.
2 weeks after the first. However, the efficacy of one application as compared with two applications has not been formally tested, and the optimal interval between doses has not been precisely defined.

Ivermectin, administered orally at a dose of 200 μg per kilogram of body weight, is an effective alternative treatment. Since ingestion of food increases the bioavailability of ivermectin by a factor of two, taking the drug with food will enhance the penetration of the drug into the epidermis. Since ivermectin is not ovicidal, it is recommended that two doses, separated by 1 to 2 weeks, be administered for the treatment of classical scabies. The serum half-life of ivermectin is 18 hours, with drug elimination occurring through metabolism in the liver and excretion of inactive metabolites through the kidneys. Adjustment of the dose is not necessary in patients with renal impairment. However, the safety of administering multiple doses of ivermectin in patients with severe liver disease has not been studied.

In the case of crusted scabies, we recommend more frequent administration of ivermectin, ranging from three to seven doses, depending on the severity of the infection (Table 1). Patients with crusted scabies should be treated concomitantly with a topical scabicide (e.g., permethrin, benzyl benzoate, or benzyl benzoate with tea-tree oil), as well as a keratolytic cream to facilitate the breakdown of skin crusts and improve penetration of the topical agent.

In the first few days after therapy for scabies is initiated, a transient exacerbation of pruritus sometimes occurs as a result of sensitization of the human host to mite antigens, with a consequent immunologic reaction. Sensitization also frequently results in delayed resolution of symptoms, leading to confusion on the part of clinical staff, patients, and families, who may misinterpret the natural course of recovery as a failure of treatment or as a sign of reinfection. To avoid this confusion, patients can be provided with information sheets that explain the treatment, alert them to the fact that resolution of pruritus may be delayed, and assure them that repeated treatment is generally unnecessary. Topical, intralesional, or systemic corticosteroid therapy can be considered for persons with nodular scabies who have persistent symptoms, provided that administration of adequate scabicidal therapy has been clearly documented.

There may be a prolonged interval between the onset of the primary infection, at which time the patient becomes infectious to others, and the onset of clinical manifestations. During this period, which can be as long as 10 weeks, the infection may be transmitted from asymptomatic hosts to the hosts’ contacts. Because of the substantial probability that subclinical infection will occur in close contacts of the host and will result in further transmission of infection from those contacts, all family members and other close physical contacts should also be treated. Bed linen and clothing should be washed in hot water, but no special processing such as autoclaving or bleaching is required. Shoes and other nonwashable items should be placed in a tightly sealed plastic bag for at least 3 days. Establishing cure ideally requires follow-up clinical assessment for at least 1 month. This allows time for lesions to heal and for any eggs and mites to reach maturity if treatment fails.

The successful control of outbreaks of scabies in institutional settings such as nursing homes requires attention to planning and logistics of therapy. Important steps in the control of outbreaks include coordinating the documentation of case subjects and their contacts; isolating persons with clinical scabies; educating residents, families, visitors, and staff; providing therapy for all residents, staff, and other potential contacts; and disinfecting objects with which persons with crusted scabies may have come into contact.

Prolonged surveillance may be required to ensure the eradication of nosocomial scabies. The specific therapy used for scabies in institutional outbreaks will vary according to availability, cost, and current drug approvals, but at least for persons with clinical cases, a second treatment dose, administered 1 to 2 weeks after the first dose, is recommended (Table 1). Successful models have included the administration of topical therapy such as permethrin or benzyl benzoate for all case subjects and their contacts, and a combination of topical therapy and oral ivermectin, with the latter considered to be important therapy for persons with crusted scabies. In the United States, the average wholesale price of a 60-g tube of 5% permethrin cream...
is approximately $30. The cost of a 3-mg tablet of ivermectin is approximately $6, which translates into a cost of about $30 for a single dose for a patient weighing 70 kg. One study estimated that between 2001 and 2005, the typical cost of treating an episode of scabies, taking into account second doses, treatment failures, and office visits, was approximately $95.

**A D V E R S E  E F F E C T S**

Permethrin is poorly absorbed through the skin, and the small percentage that is absorbed is metabolized rapidly, with elimination being virtually complete after 1 week. Owing to theoretical concerns regarding systemic absorption of permethrin in infants, it has generally been recommended that infants be treated with crotamiton or a sulfur preparation instead of permethrin. However, given the efficacy of permethrin, it is increasingly being used in children who are 2 months of age or older.

The source of the most extensive data on the adverse effects of ivermectin in nonpregnant adults is the Onchocerciasis Control Program. Through this program, more than 400 million treatments have been distributed in Africa, with some persons having received up to 20 annual treatments. When ivermectin is used to treat filarial parasites, adverse reactions occasionally occur, including fever, myalgia, malaise, and postural hypotension. These adverse reactions are probably related to the intensity of the filarial infection and the release of parasite antigen. More severe complications, including lethargy, confusion, and coma, were seen when ivermectin was administered in patients in West Africa who were heavily infected with *Loa loa*. These complications have also been attributed to the killing of the parasites rather than to a toxic effect of ivermectin. To date, the use of ivermectin to treat scabies has not been conclusively associated with any serious adverse effects. However, it is recommended that ivermectin not be administered in children who are younger than 5 years of age or in those who weigh less than 15 kg because of the lack of data on safety and theoretical concerns regarding potential neurotoxicity (see below). It is also recommended that ivermectin not be used during pregnancy. Nevertheless, reports that have documented the inadvertent administration of the drug in pregnant women have not shown an adverse outcome for the fetus.

**A R E A S  O F  U N C E R T A I N T Y**

Drug resistance is an emerging concern with acaricides. Potential mechanisms for resistance to permethrin include sodium-channel mutations in the organism that make it less susceptible to treatment, removal of the drug by an enhanced efflux pump such as P-glycoprotein, and enzymatic degradation of the drug. Potential mechanisms for resistance to ivermectin include chloride-channel mutations in the organism and enhanced P-glycoprotein expression. In vitro studies have shown that susceptibility to permethrin is progressively reduced with repeated administration, although clinical resistance remains to be documented. Clinical resistance to ivermectin has been documented, with in vitro confirmation, in two persons with crusted scabies in whom resistance developed after the administration of repeated regimens of multiple doses of ivermectin.

Central nervous system toxicity resulting in death after treatment with ivermectin is well recognized in various vertebrates. As noted above, severe neurologic effects in humans in Africa after the administration of ivermectin have been attributed to inflammatory responses to the filarial parasites that are the target of treatment. Nevertheless, there is one report of apparent excess mortality attributed to neurotoxicity when ivermectin was used in a nursing home to control an epidemic of scabies. This report has been subject to criticism on epidemiologic grounds. Nonetheless, the safety of ivermectin at the extremes of age remains to be conclusively established, although there are increasing data suggesting that the use of ivermectin in children is safe.

**G U I D E L I N E S**

The Centers for Disease Control and Prevention (CDC) provides advice on scabies and information on specific therapies for health care providers, patients, and caregivers at www.cdc.gov/scabies/hcp/index.html. This 2008 version of the CDC guidelines has useful information on the general...
management of scabies, including crusted scabies, and the management of institutional outbreaks. Guidelines for the treatment of scabies are also available in the 2006 CDC Treatment Guidelines for Sexually Transmitted Diseases. These guidelines, which are currently being updated, include advice on the off-label use of ivermectin. The United Kingdom National Guideline on the Management of Scabies Infestation from the British Association of Sexual Health and HIV was updated in 2008 and also includes information on the off-label use of ivermectin (www.bashh.org/documents/27/27.pdf). We have developed a specific guideline for the use of ivermectin in persons with crusted scabies that includes combining topical therapy with multiple doses of oral ivermectin, according to severity; this guideline is available at www.health.nt.gov.au/Centre_for_Disease_Control/Publications/CDC_Protocols/index.aspx.

RECOMMENDATIONS

The case of crusted scabies in the elderly aunt in the vignette is unusual, and although she has probably been a core transmitter in this situation, most physicians will not see cases of crusted scabies in clinical practice. The aunt requires strict isolation after admission to the hospital in order to prevent transmission of scabies to the staff, and we would treat her severe, crusted scabies as noted in Table 1. While the aunt is in the hospital, all family members and other community contacts can be assessed and treated for scabies, and the household linen, mattresses, and clothing should be washed and aired. Topical 5% permethrin can be administered in contacts who weigh less than 15 kg and in pregnant women, and topical 5% permethrin or oral ivermectin, at a dose of 200 μg per kilogram, administered with food, can be given to all other contacts. Contacts who have evident or suspected clinical scabies should have a second treatment 7 to 14 days after the first.

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