

CLINICAL THERAPEUTICS

Permethrin and Ivermectin for Scabies

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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.¹

Scabies occurs worldwide, although estimates of 300 million cases yearly are possibly exaggerated.² The infection is endemic in many impoverished communities, but prevalence rates vary widely; seasonal outbreaks and documented peaks during times of war³ are probably related to crowding and population movements.^{4,5} In some industrialized countries, scabies is endemic in economically disadvantaged populations, and outbreaks occur in nursing homes and hospitals.⁶⁻⁸

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.^{5,9,10}

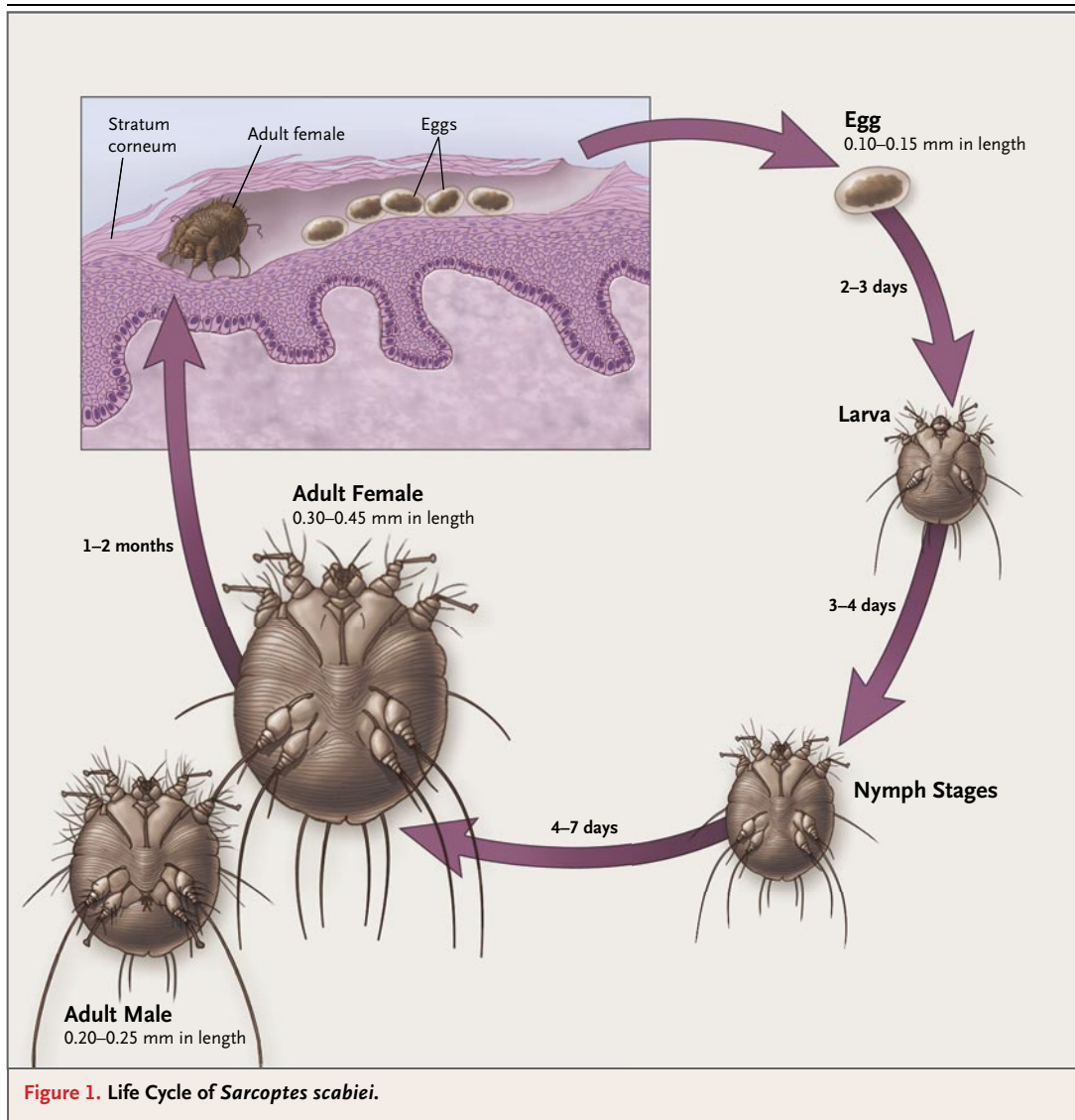
PATHOPHYSIOLOGY AND EFFECT OF THERAPY

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 inflam-

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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



Figure 2. Manifestations of Scabies.

Interdigital lesions are a typical manifestation of classic scabies (Panel A). A pattern of excoriations and pustules in the axilla is characteristic of scabies with secondary bacterial infection (Panel B). Crusted scabies can be manifested as excoriations, 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.²

been used to treat scabies. These include 5 to 10% sulfur in paraffin, an agent used widely in Africa and South America⁴; 1% lindane, which is no longer used in many Western countries because of concerns regarding neurotoxicity^{2,4}; 10 to 25% benzyl benzoate, which is often used in Europe and Australia; malathion⁷; 10% crotamiton¹²;

and 5% tea-tree oil in combination with benzyl benzoate.^{13,14}

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

membranes and disrupting neurotransmission.¹⁵ The selective neurotoxic effect of permethrin on invertebrates is due to structural differences in voltage-gated sodium channels between vertebrates and invertebrates.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.¹⁶ This interaction is well studied in nematodes, with both γ -aminobutyric acid and glutamate-gated channels identified as targets.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.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.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.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.¹⁸ A Cochrane review concluded that there are insufficient data available to compare the relative efficacies of topical permethrin and topical benzyl benzoate.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).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 involv-

ing 193 subjects, and relative risk with ivermectin as compared with benzyl benzoate, 0.50 in three trials involving 192 subjects).¹² However, a recent study showed that there was a higher rate of treatment failure with single-dose ivermectin than with topical benzyl benzoate.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.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.^{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.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.

Purpose of Therapy	Recommended Therapy	Alternative Therapy	Comments
Treatment for classic scabies	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	Two doses of oral ivermectin (200 µg/kg/dose), taken with food — one on day 1 and one between day 8 and day 15*	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
Treatment for crusted scabies	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*	Topical benzyl benzoate 25% (with or without tea-tree oil 5%) instead of permethrin	
Prevention of infection in close contacts of patients with scabies	A single application of topical permethrin 5% applied in the evening and left on overnight	Oral ivermectin (200 µg/kg/dose), taken with food, administered as a single dose*	
Management of institutional outbreak of scabies	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	For refractory outbreaks, consider treatment of all residents with oral ivermectin*	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
Prevention in communities where scabies is endemic or management of community outbreak	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	Treat persons with classic and crusted scabies, as well as contacts in the community, as recommended above	Look for “core transmitter” index cases with crusted scabies; give attention to planning and logistics of therapy; be aware that maintaining control of scabies requires addressing underlying issues of overcrowding and access to health hardware (e.g., functioning taps with clean water, sinks, and toilets in the house), health care, and education

* 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,²⁴ 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,²⁴ 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 scabicial therapy has been clearly documented.^{4,6}

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,¹ 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.⁷ 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.^{7,25-27} Prolonged surveillance may be required to ensure the eradication of nosocomial scabies.²⁸ 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,^{26,29} the administration of oral ivermectin for all residents,³⁰⁻³² and a combination of topical therapy and oral ivermectin, with the latter considered to be important therapy for persons with crusted scabies.^{8,25,27} In the United States, the average wholesale price of a 60-g tube of 5% permethrin cream

is approximately \$30.³³ 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.³³ 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 \$95.³⁴

ADVERSE EFFECTS

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.³⁵ 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,¹² 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.³⁶ When ivermectin is used to treat filarial parasites, adverse reactions occasionally occur, including fever, myalgia, malaise, and postural hypotension.³⁷ These adverse reactions are probably related to the intensity of the filarial infection and the release of parasite antigen.³⁸ 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*.³⁷ 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.²⁴ 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 inad-

vertent administration of the drug in pregnant women have not shown an adverse outcome for the fetus.³⁹⁻⁴¹

AREAS OF UNCERTAINTY

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,⁴² removal of the drug by an enhanced efflux pump such as P-glycoprotein, and enzymatic degradation of the drug.⁴³ 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,^{13,43} 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.¹⁴

Central nervous system toxicity resulting in death after treatment with ivermectin is well recognized in various vertebrates.⁴⁴ 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.³⁸ 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.⁴⁵ This report has been subject to criticism on epidemiologic grounds.⁴⁶⁻⁴⁸ 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.⁴⁹

GUIDELINES

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.⁵⁰ 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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