Dermatologic Therapy, Vol. 22, 2009, 279–292
Printed in the United States · All rights reserved

DERMATOLOGIC THERAPY
ISSN 1396-0296

Scabies

Maria I. Hicks & Dirk M. Elston
Geisinger Dermatology, Danville, Pennsylvania

ABSTRACT: Scabies is an ectoparasite caused by the mite *Sarcoptes scabiei var hominis*, an obligate human parasite. There are about 300 million cases of scabies in the world each year. Common predisposing factors are overcrowding, immigration, poor hygiene, poor nutritional status, homelessness, dementia, and sexual contact. Direct skin-to-skin contact between 15 and 20 minutes is needed to transfer the mites from one person to another. The diagnosis suspected with a clinical history of itch, worse at night, affecting other family members, clinical distribution, and appearance. Definite diagnosis relies on microscopic identification of the mites, eggs, or fecal pellets with 10% potassium hydroxide, ink enhancement, tetracycline fluorescence tests, or mineral oil; other methods include: epiluminescence light microscopy and *S. scabiei* DNA. The most commonly used treatment modalities are permethrin and ivermectin. Persistence of symptoms for 2–6 weeks after successful treatment is common. Most recurrences are because of reinfection from untreated contacts.

KEYWORDS: ivermectin, permethrin, scabies

Introduction

Scabies was first described in the Old Testament and by Aristotle. The name *Sarcoptes scabiei* is derived from the Greek word "sarx" that means flesh and "koptein" that means to cut, and the Latin word "scabere" that means to scratch. Scabies is an ectoparasite infestation; the mite itself was extracted from human skin, and recognized as the causative organism by Bonomo in 1687, and demonstrated using light microscopy in the same year and in vivo by Renucci in Paris in 1814 (1–3).

Classification

The disease is caused by the mite *S. scabiei var hominis* (2). This arthropod, *S. scabiei*, is an obligate human parasite, measuring 300–400 μm (4). It is member of the class Arachnida, subclass Acari, order Astigmata, and family Sarcoptidae. These are ovoid organisms with a small anterior cephalic and a caudal thoraco-abdominal portion with hair-like projections coming off from the rudimentary legs. They are easily distinguished from other arachnids by the position of a distinct head with mouthparts called gnatosoma, and the lack of a division between the abdomen and cephalothorax (2,5). The female mite (FIG. 1) is 0.3–0.4 mm in size, and the male mite is half the size of the female (6).

Address correspondence and reprint requests to: Maria I. Hicks, MD, Geisinger Dermatology, 115 Woodbine Lane, Danville, PA 17822, or email: mihicks@geisinger.edu.
Conflict of interest: None.

The life cycle of *S. scabiei* begins with the mating of adult male with a female mite. After mating, the adult male dies and the female mite begins to lay eggs in the skin burrow where she stays for 4–6 weeks. The female crawl at a rate of 2.5 cm/minute on warm skin, not deeper than the stratum granulosum (7), and can survive 24–36 hours at room temperature (8).

The female produces 1–3 eggs per day, hatching after 3–4 days to finally give origin to mature larvae. The larvae then pass through two further developmental stages, protonymphs and tritonymphs, before molting into either males or females. These larvae eventually cut through the roof of the burrow and reach the skin surface. The duration of the life cycle ranges between 30 and 60 days (8).

All life cycle stages can penetrate intact epidermis, by the secretion of enzymes that dissolve the skin, which is subsequently ingested. The mites can enter the skin in less than 30 minutes. During the first month of infection, the mite population up to 25 adult females after 50 days, and up to 500 mites

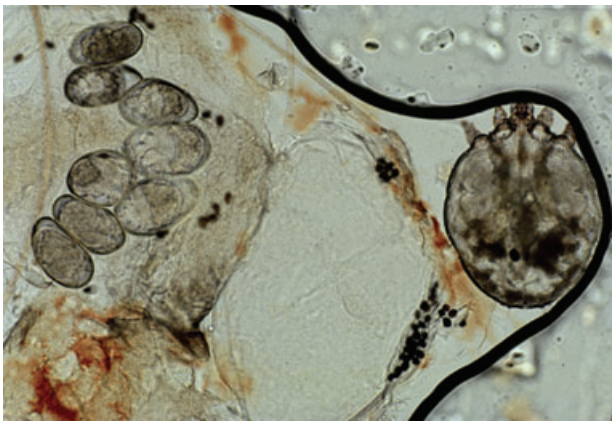

FIG. 1. Scabies mite, ova, and feces.

by 100 days (9). However, the average burden on a normal host is 10–12 mites (7). Generally, after 3 months, mite numbers decrease rapidly. Likely explanations include mechanical removal of the mites by scratching, as well as the host immune response. For example, sensitization to mite antigens can be demonstrated a month after primary infestation (9).

Epidemiology

The Royal Infirmary of Edinburgh has stored data on infectious diseases from 1815 to 2000 (10). There are about 300 million cases of scabies in the world each year (11). The reported prevalence of scabies varies from 3.8% in shelter-based investigations to 56.5% among hospitalized homeless persons. It is more prevalent in the homeless than in the general population. It is also highly prevalent in children, most commonly younger than 2 years of age and in tropical countries where scabies is endemic (12).

Scabies is most common in young children, possibly reflecting both increased exposure and, in endemic situations, lack of immunity. Both sexes are affected equally. Ethnic differences in scabies epidemiology are most likely to be related to differences in overcrowding, housing, socioeconomic, and behavioral factors, rather than racial origin. The most common predisposing factors are overcrowding, immigration, poor hygiene, poor nutritional status, homelessness, dementia, and sexual contact. Some reports in the literature have shown how scabies may represent a threat for institutional settings, mainly hospitals, prisons, kindergartens, nursing homes, and long-term care facilities (2). This is more common with heavily infested patients like in crusted scabies. A lower prevalence of infestation has been observed in African-Americans (7).

Some authors have reported fluctuations of scabies every 7 years (scabies is also termed "7-year itch"), and there are some others that report a peak every 15–25 years, for reasons yet unknown (7), except in areas where this disease is endemic, for example, South and Central America, India, South Africa, and some Australian Aboriginal communities.

Seasonality trends of scabies have been documented. Some studies have suggested higher incidence during the winter months, and the likely explanation is mites survive longer away from the body in cooler weather and colder weather encourages overcrowding in human beings (13–16). Mites also might be sensitive to antimicrobial peptides contained in human sweat, leading to reduced infestation in summer (2).

Transmission and pathogenesis

The disease is transmitted by direct skin-to-skin contact, which is why the transmission among family members is so common. It has been estimated that a patient with conventional scabies needs between 15 and 20 minutes of close contact to transfer the mites from one person to another (17).

The role of fomites is controversial; some authors claim that this can be possible because mites can survive more than 3 days outside the human body and this is supported also by the recollection of live mites from dust sample from clothing, bedding, furniture, and floors (18), but for some other authors, this transmission is uncommon (19), but may occur in cases of crusted scabies (8). The average patient can have between 5 and 12 mites, and it is higher in crusted scabies, where the patient can have millions of mites, therefore patients are more contagious especially for the medical and paramedical staff.

Sexual transmission also occurs because the sexual act provides close contact for the transmission of the mites. High-risk persons are men who have sex with men, and men with sporadic sexual contact. There are not many epidemiological studies in scabies as sexual transmitted diseases, but a prospective 15-year study conducted by Otero et al. in a STD unit in Spain found that 147 patients (1.5%) were affected by the disease, and being more frequent in males (2.1%) than in females (1.2%) ($p < 0.001$) and more common among men younger than 35 years old, who have sex with men. Additionally, among women, the disease was more common in alcohol abusers, and in those using contraceptive pills (20).

Host immune response

Once the *S. scabiei* penetrates the skin, it releases substances in response to contact with keratinocytes and Langerhans cells (21), initiating an inflammatory and immune reaction that involves multiple cell lines (22).

The reaction consists of both type I and type IV hypersensitivity reactions. In the type I reaction, an antigen on the mite encounters specific immunoglobulin-E (IgE) on mast cells within the epidermis, leading to the degranulation of mast cells causing wheal-and-flare reactions. This is supported by the fact that there is elevation of IgE antibody among scabies patients, decreasing after successful treatment (23). Additionally, cross-reactivity between the scabies mite and the house dust mite has been described (24). In the type IV hypersensitivity reaction, patients that have not had contact with the mite will have between 10 and 30 days before the rash is noticeable (23). When patients are infected for a second time, the hypersensitivity reaction may develop within a day.

Scabies exhibit strong superficial and deep dermal and perivascular inflammatory infiltrates composed of lymphocytes, histiocytes, and eosinophils, and will eventually have elevated antibody titers specific for antigens from the parasite. There is marked increase in the secretion of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), and slight increase in secretion of granulocyte colony stimulating factor (G-CSF) from normal human epidermal keratinocytes. IL-6 is known to stimulate the proliferation of keratinocytes; on the other hand, IL-8 and G-CSF promote monocytes becoming dendritic cells and the proliferation of neutrophils (25). IL-6 is also known to activate Th1 CD4+ cells to secrete IL-2, promoting their proliferation and differentiation, to activate Th2 CD4+ cells to produce IL-4, which drives antibody production known to increase vascular permeability, initiating inflammation, which explains the edema present in scabies lesions (22).

Previous studies that showed increased mitosis in keratinocytes in the basal layer of the epidermis (21,26) correlate clinically with the hyperkeratosis seen in chronic and crusted scabies.

Molecular studies

Molecular approaches have advanced substantially in the study of genetics and transmission dynamics of *S. scabiei*. Data from *S. scabiei* complementary DNA (cDNA) libraries have identified several unique genes. Among the cDNAs encoding for *S. scabiei* are homologues of the known house dust mite allergens glutathione-S transferase, paramyosin, and cathepsin-L (27).

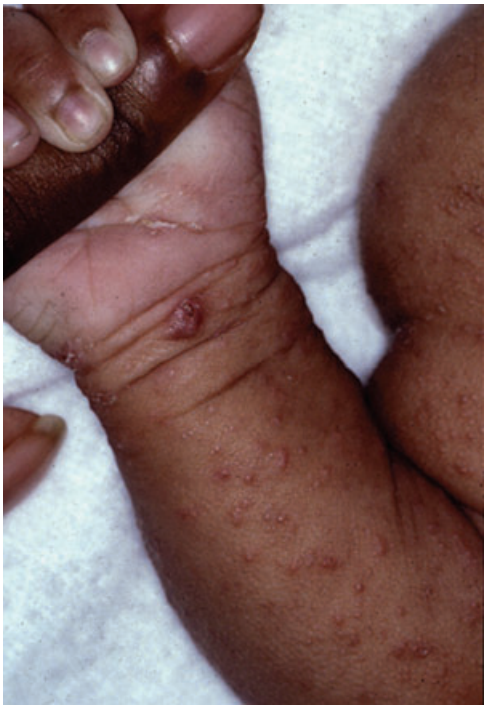

FIG. 2. Burrows and excoriations in an infant with scabies.

Clinical features

Classic scabies

The most common symptoms are produced by the host immune reaction to borrowed mites and their products. Classic scabies is typically described as an intense, intractable, generalized pruritus, worse at night, but occasionally, patients are asymptomatic (14).

Clinically, there is a small erythematous papulovesicular rash, generally symmetrical, with predilection for anterior axillary folds, nipple area in females, periumbilical skin, elbows, volar surface of the wrists, interdigital web spaces, belt line, thighs, buttocks, penis, scrotum, ankles, and, typically, spare the head, face, and neck in adults, but can be affected in infants and immunocompromised individuals.

The pathognomonic lesions are the skin burrows and scabietic nodules. The burrow is a short serpiginous gray line measuring 1–10 mm (28) that represents the tunnel where the female mite lives and is found on the hands and feet, particularly on the finger web spaces, thenar, hypothenar eminences. On the wrists (FIG. 2), discrete

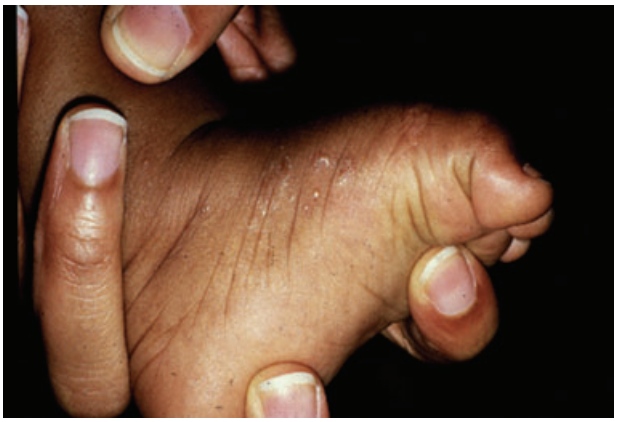

FIG. 3. Acral pustules in scabies.

burrows are rarely visible to the naked eye and lesions are often dismissed as excoriated or impetiginized skin (7).

To make the diagnosis a high index of suspicion is necessary. The clinical distribution, history of itch in other family members, at the same time, is virtually pathognomonic.

In infants and young children, scabies affect the scalp, face, and neck, but palms and soles are unique to infantile scabies (4). Very young babies do not scratch and may look miserable and feed poorly. Clinically, brownish to pinkish nodules, vesicles, often accompanied by plaques, pustules, or nodules, are found. Acral pustules are common (FIG. 3). The appearance of the rash is often altered secondary to a bacterial superinfection or topical steroid use. In adults, genital or groin nodules may predominate (FIGS. 4 and 5).

The majority of the patients will complain of an intense itch especially at night and after a hot shower. This has been associated with a hypersensitivity reaction to the excreta that the mite deposits within the burrow (29).

Nodular scabies

These nodules are violaceous, pruritic, and may persist for several months, and most commonly located on the glans, scrotum, thighs, and axilla, and mites cannot be recovered from these nodules (8). It is believed that this represents a form of hypersensitivity reaction to mite antigens developing nodules, which can be misdiagnosed as chronic lymphocytic leukemia, B-cell lymphoma or lymphomatoid papulosis (30), and urticaria pigmentosa (31), and can be treated with intralesional corticosteroids (32) or with topical pimecrolimus twice a day (33).

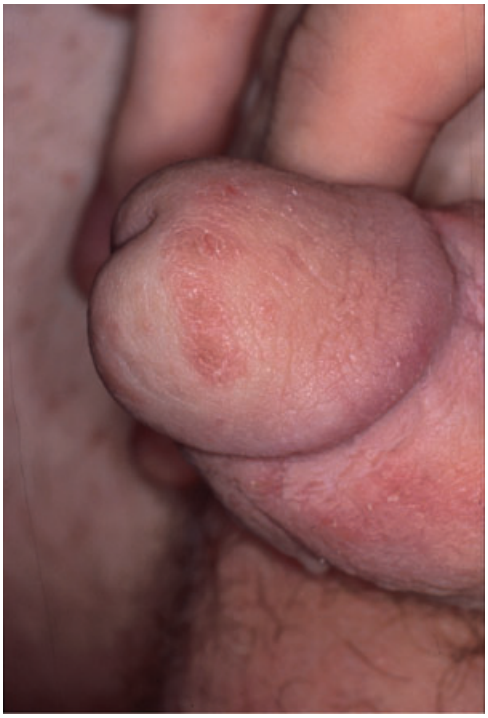

FIG. 4. Penile nodule of scabies.

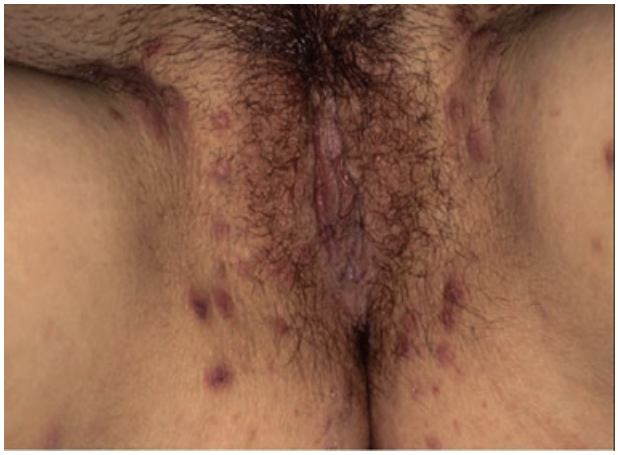

FIG. 5. Scabies nodules.

Vesicular – bullous scabies

It is a rare clinical presentation usually in the elderly. It mimics bullous pemphigoid clinically, histologically, and on immunofluorescent findings (34–36). Theories suggested that explaining the mechanism might result from superinfection with *Staphylococcus aureus*, with a mechanism similar to the development of blisters in bullous impetigo (37). Others think that the penetration of the mite in the dermo-epidermal junction, or cross-reaction with bullous pemphigoid antigen or lytic secretions produced by the mite at the dermo-

epidermal junction, may stimulate production of autoantibodies that activate the complement (38). The differential diagnosis includes pemphigoid, pemphigus, bullous impetigo, epidermolysis bullosa, arthropod bite reaction, and acute contact dermatitis (34).

Special forms of scabies

These forms are often misdiagnosed because they are atypical on its presentation.

Incognito. This is because of topical corticosteroid application and modifies the clinical aspect of lesions (32). There is an association with hypereosinophilia in the presence of mild reduction of immunity (39).

Infants and young children. They are often misdiagnosed. Clinically, lesions are more vesicles, pustules, and nodules mainly distributed on hands, feet, and body folds. Patients can be irritable and feed poorly (40). A dense Langerhans cell infiltrate may be present histologically, creating the potential for misdiagnosis as Langerhans cell histiocytosis.

Elderly. It is frequently misdiagnosed with senile pruritus, and they receive potent corticosteroid therapy for prolonged periods of time, which can lead to crusted scabies. The other type of clinical presentation is bullous scabies, which can mimic bullous pemphigoid (30,41).

Scabies of the scalp. May be associated or simulate seborrheic dermatitis or dermatomyositis. More common in elderly, children, infants, immunosupressed patients, and patient with crusted scabies (8).

Crusted. Formerly known as Norwegian scabies, the first recognition was in Norway in 1848 among patients with leprosy. This is attributable to immunosuppression (topical or systemic glucocorticoid therapy, HIV, human T lymphotropic virus 1 (HTLV-1) infection, organ transplant patients), mentally retarded, physically incapacitated (30,42,43), and indigenous Australians with no known immune deficiency.

Clinically, there are thick, gray, scaly, hyperkeratotic, or crusted plaques typically affecting hands, feet, knees, elbows, trunk, scalp, nail beds, and, sometimes, the entire body (44). Mites are commonly found beneath the nails of affected patients, and in crusted scabies, this can result in thickened dystrophic nails. In normal scabies, the distal ends of nails may harbor scabies mites, where they are protected from topical treatment (45), but in crusted scabies, larger mite populations may cause subungual hyperkeratosis and longitudinal nail splitting. Untreated nails can act as a reservoir of infection, resulting in treatment failure with recurrence of symptoms months later (46).

Generalized adenopathy and eosinophilia are present in some cases (40). Because of altered immune response in immunocompromised subjects, itch is less intense or absent in these subset of patients and/or they have physical limitation, lack of control, or unawareness of the defensive scratching movements, as in neuropsychiatric disorders, osteoarticular deformities, muscular atrophy, or other neuromuscular problems sometimes associated with loss of sensation, hypoesthesia, or anesthesia; these patients are highly infested with mites (47).

The crusts are rich in mites, and these crusts flake off and contaminate clothing, linens, curtains, walls, floor, furniture, and the immediate environment, where the mite remains infective for 2–3 days. Crusted scabies carry high mortality related to secondary sepsis (5). There was a case reported of crusted scabies in a juvenile rheumatoid arthritis patient after treatment with infliximab. This was thought to be secondary to its immunomodulatory effects in cellular immunity, which predisposed the patient to a severe infestation (48). Differential diagnosis is psoriasis (49).

Subungual scabies. This is a well-known entity but often misdiagnosed. It manifests as nail plate dystrophy, which persists even after successful treatment (50). It can affect several fingernails and/or toe nails; they have a thickened, whitened appearance with or without nail plate deformity and/or subungual horny debris. This can even be the initial manifestation of scabies (51).

Because pruritus is so constant in scabies, the scratching may catch viable mites, which can survive under the nails and then colonize the skin starting from around the nail going proximally. This will help for reinfestation in patients once they are cured. This is why it is recommended to trim the nails very short, followed by brushing of the fingertips with scabicidal on consecutive several days in addition to the regular treatment (52).

Canine. Incidence of human infection by canine scabies is unknown and is misdiagnosed as insect bites, papular urticaria. It is also an intensely pruritic rash in areas that are in contact with the pet

such as forearms, thighs, chest, and abdomen that starts within 24–96 hours after being in contact with the infected pet and is self-limited, lasting an average of 5–13 weeks. In more complicated cases, patients can present with fever, lymphadenopathy, and secondary bacterial infection. The pet is easily recognized because it presents patches of hair loss and/or scratching. There are some reports that suggest that repetitive exposure to *S. scabiei var canis* can confer some protective immunity to *var hominis*. Treatment of the dog is all that is required (53).

Differential diagnoses include atopic dermatitis, allergic contact dermatitis, lepidopterism, and fiberglass dermatitis. Scabies infestation may be misdiagnosed as adverse drug reaction (54), Langerhans cell histiocytosis (55–57), and immunobullous disease. In hot moist climates, all patients with widespread impetigo should be investigated for scabies.

Outbreaks

Scabies can be a threat in nursing homes and hospitals. Outbreaks in these settings commonly relate to a patient with crusted scabies because such patients are heavily infested with mites and often go unrecognized because of atypical presentations. Delayed isolation or noncompliance with contact precautions further contribute to the spread of the infestation. Patients with senile dementia are at higher risk for extensive skin involvement, as cognitive disorders make it difficult for individuals to communicate their symptoms and impair the scratch response (44,58).

Diagnosis

The diagnosis should be suspected in any patient with a clinical history of itch, worse at night, affecting other family members or close contacts, and can be made on the clinical distribution and appearance of skin lesions. But the definite diagnosis relies on microscopic identification of the mites, eggs, or fecal pellets (scybala) from the scrapings of the skin burrows with a scalpel blade and placing the specimen on a glass slide with 10% potassium hydroxide, ink enhancement, tetracycline fluorescence tests, or mineral oil (5,7,28). The diagnosis is made by microscopic visualization of the mite, the burrow, the excreta, or the eggs within the skin. The diagnosis becomes complicated in patients who have severe hypersensitivity reactions that result in multiple excoriations or plaques. These findings make visualization of the mite and burrow almost impossible. In such patients, biopsies or scrapings of the papule-vesicles may be helpful, as may India ink or gentian violet marking of burrows. To accomplish this, the stain is painted on the skin, and then removed with alcohol.

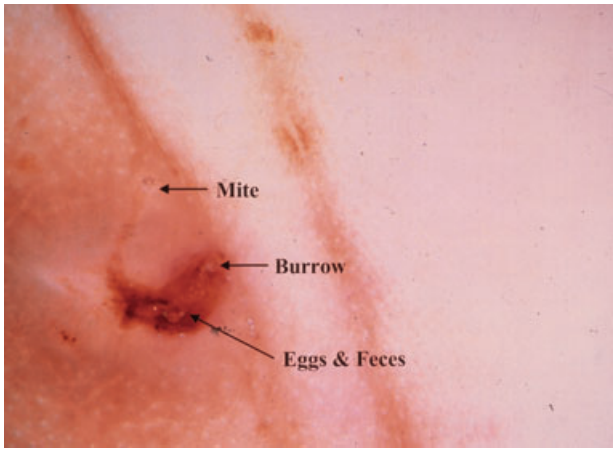

FIG. 6. Dermoscopic image of a scabies burrow (courtesy of Jeff Meffert, MD).

Newer methods to diagnose scabies include dermoscopy (FIG. 6), detecting *S. scabiei* DNA from cutaneous scales based on amplification by polymerase chain reaction (PCR) or by enzyme-linked immunosorbent assay detection. For this test, cutaneous scales are better than a skin biopsy. This noninvasive procedure may be a helpful tool in patients where scabies is highly suspicious, but diagnosis cannot be proven either clinically or by other methods such as dermoscopy or staining of burrows with water-washable ink or topical tetracycline followed by fluorescence detection with a Wood's lamp. This technique can also be used to verify that appropriate treatment was done and the mite was eradicated.

It is important to remember that *S. scabiei* DNA has to be eliminated from the corneal layer after successful treatment before executing the test again. For this reason, it is useless to repeat the test before at least 28 days because this is what usually takes the epidermal cells to transition and be eliminated, and dead scabies material should be completed after this time. Positive scabies PCR more than 28 days after completion of therapy indicates either recurrence or persistence of insufficiently treated scabies (59).

Dermoscopy (epiluminescence light microscopy, ELM) is generally performed with 10× magnification, which is applied directly onto skin lesions after paraffin oil or alcohol is applied. Newer

instruments do not require the application of a liquid interface. The fore portion of the mite appears V-shaped. This corresponds to head and two pairs of legs. This is a sensitive technique, even in inexperienced hands with acceptable specificity, and can improve treatment decision (60). Diagnosis with ELM can use higher magnification (40–1000×); here, long scabies structures can be seen, as well as eggs and feces. Both high and low magnification instruments can be used to monitor antiscabietic therapy. Before treatment, more mites are seen, average 3–24, epimeres or chitinous internal structures attached to legs, eating tools, both pairs of forelegs and hind legs are seen. After 1 week of treatment, the number of mites are reduced; after 2 weeks, the animals begin to degrade, but epimeres are more distinct especially in children; after 3 weeks of treatment, some structures are missing; and by week 4, the are no visible remains of the mites. Possible explanations for the disappearance of mites are secondary to scratching and the normal desquamation process taking place in the epidermis slowly promoting upward the mite, and that is an explanation why it is more visible after a couple of weeks after treatment (61). The limitations are that viability of mite can not be assessed, eggs are not visible, can be challenging in hairy areas, and the device needs to be carefully disinfected because mites can survive the environment up to 72 hours (60).

Treatment

The ideal treatment for scabies should be effective against adult mites and eggs, easily applicable, nontoxic, nonirritant, safe for all ages, and economical. Still, we do not have the ideal scabicide yet. See Table 1 for level of evidence.

Table 1. Scabies treatment

Medical treatment of scabies, level of evidence
Topical
Permethrin 5%[a]
Precipitated sulfur 2–10% in petrolatum[b]
Lindane (gamma benzene hexachloride 1%)[a]
Benzyl benzoate 10–25%[a]
Monosulfiram 5–25%[c]
Crotamiton 10%[a]
Malathion 0.5%[c]
Esdepallethrin 0.63%[c]
Ivermectin 1%[c]
Oral
Ivermectin[a]

[a]Good quality patient-oriented evidence.
[b]Limited quality patient-oriented evidence.
[c]Other evidence including: consensus guidelines, extrapolations from bench research, opinion, or case studies.

Topical treatments

Permethrin 5%. It is a synthetic pyrethroid and potent insecticide, which is probably the most effective topical medication for the treatment of scabies (62) and has low toxicity in mammals. Permethrin was first put on the market in 1977 and initially used for the treatment of infestations of head, crab, and body lice. It is absorbed cutaneously in small amounts and metabolized by skin esterases to be finally excreted back to the skin by sweat and sebum, and also excreted in the urine. The main factor limiting the systemic absorption is the slow penetration through the skin, which is independent of the dose that is applied (63). Its mechanism of action is disrupting the current on the sodium channels that are ubiquitous, delaying repolarization on the mite, causing paralysis and death of the parasite in all stages (64).

It comes as 5% cream, which is applied overnight or for at least 8–12 hours after which it should be washed off, and should be repeated a week later. The cream should be applied to the entire body, including the head in infants (40,65,66).

It is often used in pregnant women with application shortened to 2 hours and is widely used in young children. It is well tolerated with minimal side effect and is cosmetically acceptable. Some patients may experience some irritation, burning sensation, irritation, or tingling, but all are of short duration and most probably related to be applied on skin that is already sensitive, excoriated, and pruritic because of the scabies infection (63), also because the preservative formaldehyde might be expected to cause some allergic contact dermatitis cases. A Cochrane meta-analysis of four randomized trials comparing permethrin and lindane showed that permethrin, given as a single overnight application, was more effective than lindane (19,67). However, there was considerable heterogeneity in effects among studies. In the largest trial, there was no difference in clinical cure rates, at an average of 28 days after treatment (68). Other studies have shown that single application of permethrin has better results than a single dose of ivermectin (64). Several studies have shown that permethrin has a higher clearance rate than lindane and crotamiton (69), and less percutaneous and toxic effects when permethrin was com-

pared with lindane (70). There is one case report of congenital leukemia on a preterm female newborn after her mom heavily used permethrin on its aerosolized form while pregnant because of arachnophobia, raising concern about the safety of repeated applications (71).

Precipitated sulphur 2–10% in petrolatum. It is the oldest treatment modalities for scabies, used since 25 AD. It is safe to use in pregnancy, infants, and children (72). The ointment is applied to all body surfaces for two to three consecutive nights. It has been effective in crusted scabies and in patients' refractory to other treatments. The disadvantage resides on that it is messy, smelly, stains clothes, and can cause irritant dermatitis.

Lindane (gamma benzene hexachloride 1%). First used in 1948 by Wooldridge (73) to treat scabies, lindane acts on the mite's central nervous system (CNS), producing excitability, convulsions, and death. It is absorbed by mucous membranes, such as lung and intestinal mucosa, and is distributed to all body compartments, with the highest concentration in lipid-rich tissues and the skin. Its metabolism and excretion are through urine and feces (65). It is used as a single application with contact time of 6 hours and should be washed afterwards with soap and water, some authors recommend repeating the application 1 week after (66). The commercial presentation is 1% cream, 1% lotion, or 1% shampoo, and nonirritating and easy to apply. Absorption from skin varies from 10 to 90% depending on solvents used with a half-life of 21–26 hours (74). It should be avoided in inflamed, excoriated or denuded skin, crusted scabies (75), sick children, and infants (4). The levels in breast milk are 60 times higher than in untreated women, and this medication should be avoided during breastfeeding (65).

The disadvantage is that it can cause CNS toxicity, such as convulsions and death reported in children or infants with overexposure or an altered skin barrier, which increases absorption. There is also a report of an elderly patient that died after treatment with lindane, after it was applied to the head (76). Accidental ingestion can lead to lindane poisoning because it is absorbed by mucosa, causing neurological symptoms that include convulsions, twitching of eyelids, restlessness, dizziness, headache, nausea, vomiting, weakness, tremors, disorientation, respiratory failure, coma, and death. Some other authors reveal that the risk of neurotoxicity is minimal if used properly and strictly according to the prescribed recommendations. Ulcerative irritant contact dermatitis from the use of lindane was reported (77). There is some evidence that lindane may cause aplastic anemia, thrombocytopenia, and pancytopenia (78). The US Food and Drug Administration (FDA) has recommended lindane as a second-line therapy for scabies and pediculosis mainly in young children, elderly, and people weighing less than 50 kg because all side effects are more common in this population (79,80). It is banned in California.

Benzyl benzoate 10–25%. This is an ester of benzoic acid and benzyl alcohol obtained from balsam of Peru and Tolu, which is neurotoxic to the mites. It is used as a 25% emulsion applied below the neck three times within 24 hours with contact time of 24 hours, without rinsing the product. In young adults or children, the dosage can be reduced to 12.5%. It is very effective when used correctly, and if not, it may lead to treatment failure or cause irritant dermatitis on the face and scrotum. Its use may be complicated by allergic dermatitis (81). This product is not safe to use in pregnancy, lactating women, infants, and children less than 2 years of age because its use has been associated with severe neurological side effects in children (65). Some studies have found it to be effective in the management of permethrin-resistant crusted scabies, and in combination with ivermectin in patients with relapses after a single treatment with ivermectin. In developing countries where the resources are limited, it is used in the management of scabies as a cheaper alternative (4,81).

Monosulfiram 5–25%. It is chemically related to antabuse, and for this reason, alcoholic beverages should be avoided during or earlier after treatment, at least 48 hours because it inhibits hepatic aldehyde dehydrogenase and after ethanol ingestion, the acetaldehyde accumulates causing a spectrum of undesirable side effects including flushing, nausea, vomiting, and tachycardia, which are referred to as the disulfiram reaction (82). It is applied all over the body after a bath, and it should be rubbed once a day for two or three consecutive days. Soaps containing monosulfiram have been used in the past as a prophylactic measure in infected communities (83). One study compared the effectiveness of oral ivermectin 200 mcg/kg with topical 25% benzyl benzoate and monosulfiram soap, and showed that ivermectin was at least as effective and led to more rapid improvement (84).

Crotamiton 10%. Crotonyl-N-ethyl-o-toluidine is used after bathing and changing clothes as 10%

cream or lotion applied twice a day for five consecutive days, and contact period has to be 48 hours. The efficacy varies between 50 and 70%. It can be useful for the treatment of scabies nodules in children (30). While it is commonly used as an antipruritic, recent studies have questioned whether it has specific antipruritic effects (66). Some authors do not recommend crotamiton because of the lack of efficacy and toxicity data (11).

Malathion 0.5%. It is an organophosphate insecticide that irreversibly blocks the enzyme acetylcholinesterase. Malathion is commonly used to treat pediculosis, but there is little information pertaining to its use in scabies (65).

Esdepallethrin 0.63%. It is a synthetic pyrethroid that targets sodium channels at the axons. It is aerosol and can be used in infants older than 2 years old (30).

Ivermectin 1%. There is one uncontrolled, open label trial study published using topical ivermectin 400 mcg/kg/dose on 10 mL of propylene glycol applied to body surface on major flexure waist area, genitals, hands, and feet. Patients avoided taking a bath for 2 hours, and this was repeated 1 week later. Treatment of clothes, fomites, and households were recommended. From 32 patients, 12 adults and 20 children, 29 were cured; there were no signs of recurrence 2, 4, 6 weeks after treatment and there were no side effects (85).

Oral treatments

Ivermectin

Ivermectin, the 22, 23 dihydro-derivative of avermectin B_1, is a synthetic of macrocyclic lactones known as avermectins, with structure similar to macrolides, but without any antimicrobial action. It was developed in 1970s as a veterinary agent (86). In the United States, it is licensed for use for *Strongyloides* infections. Also, it has been used in humans to treat scabies, onchocerciasis, other filariases, and intestinal nematodal infections (87).

Ivermectin binds selectively to receptors in the peripheral motor synapses, blocking chemical transmission of γ-aminobutyric acid (GABA)-gated chloride channels localized in the CNS. This stimulates the discharge of GABA at the nerve endings of endoparasites, increasing the affinity of GABA in the receptor at synapses and causing interruption of the nerve impulses, producing paralysis and death to parasites (88).

Ivermectin is absorbed easily on an empty stomach, has hepatic metabolism, and is mostly fecal excretion. The peak is around 4–5 hours postingestion and has a half-life of 36 hours. Peak concentration is found in sebum, sweat, and squames of forehead 8 hours after first dose (89).

Ivermectin is relatively safe. It has been tested in vitro in microbial and mammalian cell assays showing no genotoxic activity. Primates, including humans, are clearly less sensitive than mice, being more toxic in infant than young adult rats (88). Treatment with very high dosages of ivermectin caused embryotoxicity in animals (90). The adverse reactions include fever, headache, chills, arthralgia, rash, eosinophilia, and anorexia. Many of these symptoms are thought to result from the death of parasites rather than as a reaction to the drug (91). Other more serious adverse effects are ataxia, tremors, mydriasis, depression, and, in severe cases, coma and death (30).

Ivermectin is not only used for treatment of ectoparasites that cause scabies but also head lice, human body lice, demodecidosis, and endoparasites causing cutaneous larva migrans, myasis, furuncular myasis, strongyloidiasis, filariasis, and onchocerciasis in animals and humans (88).

Parasitic resistance to ivermectin has been reported in nematodes of horses, sheep, and other animals after almost 20 years of use (92,93), through either alteration of a membrane protein that actively transports the drug across cell membranes, the P-glycoprotein, or through alteration of the chloride channel receptor (94).

Ivermectin is given orally 200 mcg/kg in most patients as a single oral dose preferably in the evening, when the mites stray over the body (89,95). Ivermectin has a plasmatic half-time after it is orally administered (36 hours), and it is believed that mites feed by ingesting keratinocytes and intercellular fluids within the epidermis rich in ivermectin, so it will be effective against fertile tunneling mites; because it is believed that ivermectin does not have ovicidal properties and because the eggs hatch every 6–7 days, it is recommended to repeat the treatment two or three times, separated by intervals of 1 or 2 weeks (64,96).

A double-blind study showed that 79.3% of patients with scabies were cured 1 week after a single oral dose of 200 μg/kg of ivermectin, as compared with 15.4% of patients in a placebo group (97) with mild to moderate scabies, but is preferable to use ivermectin in combination with benzyl benzoate solution in crusted scabies occurring

in HIV/acquired immune deficiency syndrome patients (98). It was shown to be effective compared with placebo (19,97). Some authors achieved only 80% success rates with 200 mg/kg of the drug, and some increase the dosage to 250 mcg/kg (96).

Other randomized, controlled trials of treatment with ivermectin versus benzyl benzoate and ivermectin versus lindane failed to demonstrate significant differences in clinical cure rates (99). Another study that compared a single dose of ivermectin 200 mcg/kg and lindane 1% lotion showed that 83% of the patients in the ivermectin group had marked improvement compared with only 44% of the patients in the lindane group (100). Studies comparing ivermectin and permethrin showed that a single dose of ivermectin provided a cure rate of 70%, which increased to 95% with two doses at a 2-week interval. A single application of permethrin was effective in 97.8% of patients (64).

Ivermectin has been successfully employed to eradicate scabies in epidemic or endemic situations in institutions such as nursing homes (69,101,102) and prisons (103). Because of its ease of use, some use it as the first-line treatment for cases of scabies in adult nursing homes and institutions, although one report suggested that it could contribute to mortality in an elderly population (104).

Oral ivermectin offers several advantages over standard topical scabicides (75,105,106) such as high efficacy, ease, and rapidity of application, avoiding the irritation caused by topical treatments and avoiding the need to ensure proper application; and it is well tolerated – all these help with patient compliance. It is convenient for persons who are bedridden and immunocompromised (106). Ivermectin is an effective treatment for scabies in closed communities, such as a prison (103), and reduces occurrence of streptococcal disease and possible signs of renal damage in children (107).

To avoid outbreaks, some recommendations should be followed such as using proper barrier precautions like gloves with extended cuffs; patients receiving two treatments before isolation is discontinued; developing identification, reporting, and treatments from health care workers to hospital and clinical personnel; and treating all exposed staff if there is prolonged skin contact if scabies is present or there is contact in patients with crusted scabies (44,108). In this setting, ivermectin is an effective and easy treatment to administer, avoiding problems with compliance although it is of limited efficacy on crusted scabies (103).

Treatment tips

1. Proper application must be achieved including the umbilicus, genitalia, up to the edge of all body orifices, and under the free edges of nails.
2. There is data suggesting that fomites are important in the spread of scabies (18). Populations of mites have been recovered from linens, chairs, floor, dust, etc (109). For practical purposes, it is probably not necessary to do anything beyond laundering of sheets and clothing, although some also suggest vacuuming couches.
3. Close physical contacts of infested patients spread the disease. Parents, caregivers, people involved in bathing or lifting (110), sexual partners, and family members are at high risk of acquiring the infection and all should be treated at the same time regardless of symptomatology (111). It is estimated that 15–20 minutes of close contact with an infected patient is enough to transfer the mites from one person to another (17).
4. People that are reinfected are at risk of cumulative drug toxicity (111).
5. Prisons, nursing homes, daycare centers, and hospital wards may experience epidemics or scabies breakouts that are difficult to treat because of delayed diagnosis. Here, it is imperative to treat all residents, patients, staff, and frequent visitors at the same time, even if they are not symptomatic, in order to control infestation (111,112).
6. We recommend washing bed linens and clothing. Clothes and bed linens can be machine washed at 60°C followed by heated drying (8,113). Clothes that cannot be washed should be kept on a bag for at least 3 days, because some studies have documented that mites cannot survive more than 3 days after separation from their human hosts (114). In humid climates, they may survive much longer. Vacuuming can be of benefit, but the benefits of environmental acaricides remains to be established (111).
7. In the setting of crusted scabies, the use of insecticidal powders or aerosols may be considered for materials that cannot be washed (30), or simply isolated.

Special situations

Crusted scabies will require admission to hospital in most cases. Scabicides should be applied from head to toe. Keratolytics may improve penetration of treatment agents. Nails should be trimmed

and brushed with a scabicidal agent. Generally, with topical treatments, cure is reached after three consecutive treatments, but sometimes, patients will require additional treatments. Our experience is that 10% precipitated sulfur in petrolatum is more reliable that permethrin in this setting. Oral ivermectin can be used alone, but is more effective in combination with topical treatment (115,116). Institute barrier precautions to prevent dissemination.

In the elderly, immunocompromised, and infants up to 2 years of age, the topical treatments should also be applied to scalp, neck, face, and ears.

In infants, sulfur 2–10% in petrolatum can be used (66). Permethrin 5% cream is approved for use only in infants older than 2 months (65,117). There is a report where oral ivermectin in combination with lindane and keratolytics cleared an 11-year-old girl with crusted scabies without any side effects, but it should be noted that lindane absorption may be increased in this setting (118). Where available, benzyl benzoate is a cheaper alternative to permethrin, and can be diluted to 12.5% emulsion and can be used topically.

In pregnant and lactating women, 6% sulfur precipitate is recommended by some authors because of the possible association between permethrin and leukemia noted previously. It should be noted that little has been published about the potential toxicity of sulfur. Ivermectin crosses the blood–brain barrier poorly in mammals, but this can be deficient in young mammals, which could allow greater penetration to the CNS (65,109,118).

A study in elderly patients reported increase in death among patients using ivermectin, but it has not been confirmed in other trials (92). Elderly patients with recalcitrant crusted scabies unresponsive to multiple topical treatments of lindane, permethrin, and crotamiton were treated with a single 200 mcg/kg dose of ivermectin. Many of the patients suffered from dementia and were housed in a single closed ward of a long-term care facility. Patient deaths were reported, but no cause of death was established, and analysis by the FDA and the World Health Organization onchocerciasis program questioned a connection between these deaths and ivermectin use (119).

To avoid outbreaks, some recommendations should be followed such as using proper barrier precautions like gloves with extended cuffs. Patients should receive two treatments before isolation is discontinued. Institutions should develop identification, reporting, and treatment recommendation. It is important to treat all exposed staff if there has been prolonged skin contact, especially with patients with crusted scabies (44,108).

Resistance

There is well-documented resistance to topical therapy and this is an increasing problem worldwide. It has been reported with lindane, and in clinical and in vitro evidence of ivermectin resistance in patients with multiple recurrences of crusted scabies who had previously received 30–58 doses of ivermectin over 4 and 4.5 years that this can be developed after intensive ivermectin use (120,121).

Persistent symptoms

It is normal for patients to experience persistence of symptoms for 2–6 weeks after successful treatment. This is because of the immune response elicited against the mite antigens. If the symptoms persist beyond 2 weeks, it could be because of incorrect initial diagnosis, incorrect application of treatment and poor penetration of treatment through thick scales, reinfection, or drug-resistant mites (5). Most recurrences are because of reinfection from untreated contacts. It has also been suggested that pruritus can worsen temporarily after treatment secondary to massive death of mites and the release of their toxic products (122).

Conclusion

Scabies persists as a worldwide pandemic. Because of its protean manifestations, it remains one of the most commonly misdiagnosed of dermatologic maladies. In the young, it may present with acral pustules, bullae, or papules composed of sheets of Langerhans cells. In the elderly, it mimics immunobullous disease and is a common cause of cryptic pruritus. The savvy dermatologist knows that scabies and tinea should be appended to most differential diagnosis lists. A high index of suspicion will serve both the patient and clinician well.

References

1. Parish LC. History of scabies. In: Orkin M, Maibach HI, Parish LC, Schwartzman RM, eds. Scabies and pediculosis. Philadelphia: Lippincott, 1977: 1–7.

2. Hengge UR, Currie BJ, Jager G, Lupi O, Schwartz RA. Scabies: a ubiquitous neglected skin disease. Lancet Infect Dis 2006: **6**: 769–779.
3. Mathisen GE. Of mites and men – lessons in scabies for the infectious diseases clinician. Clin Infect Dis 1998: **27**: 646–648.
4. Karthikeyan K. Treatment of scabies: newer perspectives. Postgrad Med J 2005: **81**: 7–11.
5. McCarthy JS, Kemp DJ, Walton SF, Currie BJ. Scabies: more than just an irritation. Postgrad Med J 2004: **80**: 382–387.
6. Angeles RM. A closer look at *Sarcoptes scabiei*. Arch Pathol Lab Med 2005: **129**: 810.
7. Johnston G, Sladden M. Scabies: diagnosis and treatment. BMJ 2005: **17**: 619–622.
8. Chosidow O. Clinical practices. Scabies. N Engl J Med 2006: **354** (16): 124–129.
9. Mellanby K. Scabies in 1976. R Soc Health J 1977: **97**: 32–36, 40.
10. Savin JA. Scabies in Edinburgh from 1815 to 2000. J R Soc Med 2005: **98**: 124–129.
11. Orkin M. Scabies: what's new? Curr Probl Dermatol 1995: **22**: 105–111.
12. Badiaga S, Menard A, Tissot Dupont H, et al. Prevalence of skin infections in sheltered homeless. Eur J Dermatol 2005: **15**: 382–386.
13. Mimouni D, Ankol OE, Davidovitch N, Gdalevich M, Zangvil E, Grotto I. Seasonality trends of scabies in a young adult population: a 20-year follow-up. Br J Dermatol 2003: **149**: 157–159.
14. Wendel K, Rompalo A. Scabies and pediculosis pubis: an update of treatment regimens and general review. Clin Infect Dis 2002: **35** (Suppl. 2): S146–S151.
15. Downs AM, Harvey I, Kennedy CT. The epidemiology of head lice and scabies in the UK. Epidemiol Infect 1999: **122** (3): 471–477.
16. Downs AM. Seasonal variation in scabies. Br J Dermatol 2004: **150** (3): 602–603.
17. Service MW. Medical entomology for students. London: Chapman & Hall, 1996.
18. Arlian LG, Estes SA, Vyszenski-Moher DL. Prevalence of *Sarcoptes scabiei* in the homes and nursing homes of scabietic patients. J Am Acad Dermatol 1988: **19** (5 Pt 1): 806–811.
19. Walker GJ, Johnstone PW. Interventions for treating scabies. Cochrane Database Syst Rev 2000: **2**: CD000320.
20. Otero L, Varela JA, Espinosa E, et al. *Sarcoptes scabiei* in a sexually transmitted infections unit: a 15-year study. Sex Transm Dis 2004: **31** (12): 761–765.
21. Stemmer BL, Arlian LG, Morgan MS, Rapp CM, Moore PF. Characterization of antigen presenting cells and T-cells in progressing scabietic skin lesions. Vet Parasitol 1996: **67** (3–4): 247–258.
22. Arlian LG, Morgan MS, Neal JS. Modulation of cytokine expression in human keratinocytes and fibroblasts by extracts of scabies mites. Am J Trop Med Hyg 2003: **69** (6): 652–656.
23. Dahl MV. The immunology of scabies. Ann Allergy 1983: **51** (6): 560–566.
24. Hermes B, Worm M, Nowak F, Kroczek RA, Stein H, Henz BM. Upregulation of CD40 and CD40 ligand expression in IgE-associated cutaneous diseases. Acta Derm Venereol 1997: **77** (6): 441–445.
25. Arlian LG, Morgan MS, Vyszenski-Moher DL, Stemmer BL. *Sarcoptes scabiei*: the circulating antibody response and induced immunity to scabies. Exp Parasitol 1994: **78**: 37–50.
26. Arlian LG, Rapp CM, Vyszenski-Moher DL, Morgan MS. *Sarcoptes scabiei*: histopathological changes associated with acquisition and expression of host immunity to scabies. Exp Parasitol 1994: **78** (1): 51–63.
27. Fischer K, Holt DC, Harumal P, Currie BJ, Walton SF, Kemp DJ. Generation and characterization of cDNA clones from *Sarcoptes scabiei* var. hominis for an expressed sequence tag library: identification of homologues of house dust mite allergens. Am J Trop Med Hyg 2003: **68** (1): 61–64.
28. Burkhart CG, Burkhart CN, Burkhart KM. An epidemiologic and therapeutic reassessment of scabies. Cutis 2000: **65**: 233–240.
29. Stricker T, Sennhauser FH. Visual diagnosis: a family that has an itchy rash. Pediatr Rev 2000: **21** (12): 428–431.
30. Chosidow O. Scabies and pediculosis. Lancet 2000: **355** (9206): 819–826.
31. Mauleon-Fernandez C, Saez-de-Ocariz M, Rodriguez-Jurado R, Duran-McKinster C, Orozco-Ovarrubias L, Ruiz-Maldonado R. Nodular scabies mimicking urticaria pigmentosa in an infant. Clin Exp Dermatol 2005: **30** (5): 595–596.
32. Sarkar R, Kanwar AJ. Three common dermatological disorders in children (scabies, pediculosis and dermatophytoses). Indian Pediatr 2001: **38** (9): 995–1008.
33. Almeida HL Jr. Treatment of steroid-resistant nodular scabies with topical pimecrolimus. J Am Acad Dermatol 2005: **53** (2): 357–358.
34. Shahab RK, Loo DS. Bullous scabies. J Am Acad Dermatol 2003: **49** (2): 346–350.
35. Brar BK, Pall A, Gupta RR. Bullous scabies mimicking bullous pemphigoid. J Dermatol 2003: **30** (9): 694–696.
36. Said S, Jay S, Kang J, Liem WH, Jensen JL, Jeffes EW 3rd. Localized bullous scabies. Uncommon presentation of scabies. Am J Dermatopathol 1993: **15** (6): 590–593.
37. Herman PS. Letter: scabies and bullae. JAMA 1975: **231** (11): 1134 (Ansarin H, Jalali MH, Mazloomi S, Soltani-Arabshahi R, Setarehshenas R. Scabies presenting with bullous pemphigoid-like lesions. Dermatol Online J 2006: **12** (1): 19.
38. Konishi N, Suzuki K, Tokura Y, Hashimoto T, Takigawa M. Bullous eruption associated with scabies: evidence for scabetic induction of true bullous pemphigoid. Acta Derm Venereol 2000: **80** (4): 281–283.
39. Haim A, Grunwald MH, Kapelushnik J, Moser AM, Beigelman A, Reuveni H. Hypereosinophilia in red scaly infants with scabies. J Pediatr 2005: **146** (5): 712.
40. Chosidow O. Scabies and pediculosis. Lancet 2000: **355** (9206): 819–826.
41. Wilson MM, Philpott CD, Breer WA. Atypical presentation of scabies among nursing home residents. J Gerontol A Biol Sci Med Sci 2001: **56** (7): M424–M427.
42. Blas M, Bravo F, Castillo W, et al. Norwegian scabies in Peru: the impact of human T cell lymphotropic virus type I infection. Am J Trop Med Hyg 2005: **72** (6): 855–857.
43. Brites C, Weyll M, Pedroso C, Badaro R. Severe and Norwegian scabies are strongly associated with retroviral (HIV-1/HTLV-1) infection in Bahia, Brazil. AIDS 2002: **16** (9): 1292–1293.
44. Obasanjo OO, Wu P, Conlon M, et al. An outbreak of scabies in a teaching hospital: lessons learned. Infect Control Hosp Epidemiol 2001: **22** (1): 13–18.

45. Witkowski JA, Parish LC. Scabies. Subungual areas harbor mites. JAMA 1984: **252**: 1318–1319.
46. Weatherhead SC, Speight EL. Crusted scabies as a cause of longitudinal nail splitting. Clin Exp Dermatol 2004: **29** (3): 315.
47. Cestari SC, Petri V, Rotta O, Alchorne MM. Oral treatment of crusted scabies with ivermectin: report of two cases. Pediatr Dermatol 2000: **17** (5): 410–414.
48. Pipitone MA, Adams B, Sheth A, Graham TB. Crusted scabies in a patient being treated with infliximab for juvenile rheumatoid arthritis. J Am Acad Dermatol 2005: **52** (4): 719–720.
49. Gach JE, Heagerty A. Crusted scabies looking like psoriasis. Lancet 2000: **56** (9230): 650.
50. Kocsard E. The dystrophic nail of keratotic scabies. Am J Dermatopathol 1984: **6** (3): 308–309.
51. Isogai R, Kawada A, Aragane Y, Tezuka T. Nail scabies as an initial lesion of ordinary scabies. Br J Dermatol 2002: **147** (3): 603.
52. Scher RK. Subungual scabies. J Am Acad Dermatol 1985: **12** (3): 577–578.
53. Burroughs RF, Elston DM. What's eating you? Canine scabies. Cutis 2003: **72** (2): 107–109.
54. Almond DS, Green CJ, Geurin DM, Evans S. Lesson of the week: Norwegian scabies misdiagnosed as an adverse drug reaction. BMJ 2000: **320** (7226): 35–36.
55. Janik-Moszant A, Tomaszewska R, Szczepanski T, Sonta-Jakimczyk D, Pobudejska A. Infantile scabies or Langerhans cell histiocytosis? Med Pediatr Oncol 2003: **40** (2): 111–112.
56. Burch JM, Krol A, Weston WL. *Sarcoptes scabiei* infestation misdiagnosed and treated as Langerhans cell histiocytosis. Pediatr Dermatol 2004: **21** (1): 58–62.
57. Tidman MJ, Adamson B, Allan S, Wallace WH. Childhood scabies mistaken for Langerhans cell histiocytosis. Clin Exp Dermatol 2003: **28** (1): 111–112.
58. Tsutsumi M, Nishiura H, Kobayashi T. Dementia-specific risks of scabies: retrospective epidemiologic analysis of an unveiled nosocomial outbreak in Japan from 1989–90. BMC Infect Dis 2005: **5**: 85.
59. Bezold G, Lange M, Schiener R, et al. Hidden scabies: diagnosis by polymerase chain reaction. Br J Dermatol 2001: **144** (3): 614–618.
60. Dupuy A, Dehen L, Bourrat E, et al. Accuracy of standard dermoscopy for diagnosing scabies. J Am Acad Dermatol 2007: **56** (1): 53–62.
61. Haas N, Sterry W. The use of ELM to monitor the success of antiscabietic treatment. Epiluminescence light microscopy. Arch Dermatol 2001: **137** (12): 1656–1657.
62. Strong M, Johnstone PW. Interventions for treating scabies. Cochrane Database Syst Rev 2007: **3**: CD000320.
63. Meinking TL, Taplin D. Safety of permethrin vs lindane for the treatment of scabies. Arch Dermatol 1996: **132** (8): 959–962.
64. Usha V, Gopalakrishnan Nair TV. A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. J Am Acad Dermatol 2000: **42** (2 Pt 1): 236–240.
65. Roos TC, Alam M, Roos S, et al. Pharmacotherapy of ectoparasitic infections. Drugs 2001: **61**: 1067–1088.
66. Hogan DJ, Schachner L, Tanglertsampam C. Diagnosis and treatment of childhood scabies. Pediatr Clin North Am 1990: **38**: 941–956.
67. Bigby M. A systematic review of the treatment of scabies. Arch Dermatol 2000: **136**: 387–389.
68. Schultz MW, Gomez M, Hansen RC, et al. Comparative study of 5% permethrin cream and 1% lindane lotion for the treatment of scabies. Arch Dermatol 1990: **126**: 167–170.
69. Paasch U, Haustein UF. Management of endemic outbreaks of scabies with allethrin, permethrin and ivermectin. Int J Dermatol 2000: **39**: 463–470.
70. Franz TJ, Lehman PA, Franz SF, Guin JD. Comparative percutaneous absorption of lindane and permethrin. Arch Dermatol 1996: **132** (8): 901–905.
71. Borkhardt A, Wilda M, Fuchs U, Gortner L, Reiss I. Congenital leukaemia after heavy abuse of permethrin during pregnancy. Arch Dis Child Fetal Neonatal Ed 2003: **88** (5): F436–437.
72. Pruksachatkunakorn C, Damrongsak M, Sinthupuan S. Sulfur for scabies outbreaks in orphanages. Pediatr Dermatol 2002: **19** (5): 448–453.
73. Wooldridge WE. The gamma isomer of hexachlorocyclohexane in the treatment of scabies. J Invest Dermatol 1948: **10**: 363–366.
74. Porto I. Antiparasitic drugs and lactation: focus on antihelmintics, scabicides, and pediculicides. J Hum Lact 2003: **19** (4): 421–425.
75. Meinking TL, Elgart GW. Scabies therapy for the millennium. Pediatr Dermatol 2000: **17** (2): 154–156.
76. Katsumata K, Katsumata K. Norwegian scabies in an elderly patient who died after treatment with gammaBHC. Intern Med 2003: **42** (4): 367–369.
77. Yu KJ, Chen HH, Chang YC, Hong HS, Ho HC. Ulcerative irritant contact dermatitis from lindane. Contact Dermatitis 2005: **52** (2): 118–119.
78. Rauch AE, Kowalsky SF, Leser TS, et al. Gamma benzene hexachloride (Kwell) induced aplastic anemia. Arch Intern Med 1990: **150**: 2393–2395.
79. Singal A, Thami GP. Lindane neurotoxicity in childhood. Am J Ther 2006: **13** (3): 277–280.
80. Wooltorton E. Concerns over lindane treatment for scabies and lice. CMAJ 2003: **168** (11): 1447–1448.
81. Anderson BM, Haughen H, Rasch M, et al. Outbreak of scabies in Norwegian nursing homes and home care patients: control and prevention. J Hosp Infect 2000: **45**: 160–164.
82. Mays DC, Nelson AN, Benson LM, Johnson KL, Naylor S, Lipsky JJ. Photolysis of sulfiram: a mechanism for its disulfiram-like reaction. Biochem Pharmacol 1994: **48** (10): 1917–1925.
83. Reid HF, Thorne CD. Scabies infestation: the effect of intervention by public health education. Epidemiol Infect 1990: **105** (3): 595–602.
84. Sule HM, Thacher TD. Comparison of ivermectin and benzyl benzoate lotion for scabies in Nigerian patients. Am J Trop Med Hyg 2007: **76** (2): 392–395.
85. Victoria J, Trujillo R. Topical ivermectin: a new successful treatment for scabies. Pediatr Dermatol 2001: **18** (1): 63–65.
86. Blair LS, Campbell WC. Efficacy of ivermectin against *Dirofilaria immitis* larvae in dogs 31, 60, and 90 days after injection. Am J Vet Res 1980: **41** (12): 2108.
87. Greene BM, Taylor HR, Cupp EW, et al. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. N Engl J Med 1985: **313** (3): 133–138.
88. Dourmishev AL, Dourmishev LA, Schwartz RA. Ivermectin: pharmacology and application in dermatology. Int J Dermatol 2005: **44** (12): 981–988.

89. Haas N, Lindemann U, Frank K, Sterry W, Lademann J, Katzung W. Rapid and preferential sebum secretion of ivermectin: a new factor that may determine drug responsiveness in patients with scabies. Arch Dermatol 2002: **138** (12): 1618–1619.
90. Paul JM. Effects of perinatal ivermectin on behavioral development of rats. Neurotoxicol Teratol 1988: **10**: 267–272.
91. Fawcett RS. Ivermectin use in scabies. Am Fam Physician 2003: **68** (6): 1089–1092.
92. del Guidice P, Marty P. Ivermectin. A new therapeutic weapon in dermatology? Arch Dermatol 1999: **135**: 705–706.
93. Walter PJ, Echevarria F, Eddi C, et al. The prevalence of antihelminthic resistance in nematode parasites of sheep in southern Latin America: general overview. Vet Parasitol 1996: **62**: 181–187.
94. Xu M, Molento M, Blackhall W, et al. Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog. Mol Biochem Parasitol 1998: **92**: 327–335.
95. Baraka OZ, Mahmoud BM, Marschke CK, et al. Ivermectin distribution in the plasma and tissues of patients infected with *Onchocerca volvulus*. Eur J Clin Pharmacol 1996: **50**: 407–410.
96. Burkhard CN, Burjhart CG. Ivermectin: a few caveats are warranted before initiating therapy for scabies. Arch Dermatol 1999: **135**: 1549–1550.
97. Macotela-Ruiz E, Pefia-Gonzalez G. The treatment of scabies with oral ivermectin. Gaceta Med Mexico 1993: **29**: 201–205.
98. Allmerica F, Pagan L, Ratty G, Vaile P. Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies. Br J Dermatol 2000: **142** (5): 969–972.
99. Chouela EN, Abeldano AM, Pellerano G, et al. Equivalent therapeutical efficacy and safety of ivermectin and lindane in the treatment of human scabies. Arch Dermatol 1999: **135**: 651–655.
100. Madan V, Jaskiran K, Gupta U, et al. Oral ivermectin in scabies patients: a comparison with 1% topical lindane lotion. J Dermatol 2001: **28**: 481–484.
101. Sullivan JR, Watt G, Barker B. Successful use of ivermectin in the treatment of endemic scabies in a nursing home. Australas J Dermatol 1997: **38**: 137–140.
102. Marty P, Gari-Toussaint M, Le Fichoux Y, et al. Efficacy of ivermectin in the treatment of an epidemic of sarcoptic scabies [letter]. Ann Trop Med Parasitol 1994: **7**: 453.
103. Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. Br J Dermatol 2000: **143**: 520–523.
104. Altman JS. Ivermectin for scabies. Arch Dermatol 1999: **135**: 1350.
105. Elmogy M, Fayed H, Marzok H, et al. Oral ivermectin in the treatment of scabies. Int J Dermatol 1999: **38**: 926–928.
106. Dourmishev A, Serafimova D, Dourmishev L. Efficacy and tolerance of oral ivermectin in scabies. J Eur Acad Dermatol Venereol 1998: **11**: 247–251.
107. Lawrence G, Leafasia J, Sheridan J, et al. Control of scabies, skin sores and hematuria in children in the Solomon Islands: another role for ivermectin. Bull World Health Organ 2005: **83** (1): 34–42. Epub January 21, 2005.
108. de Beer G, Miller MA, Tremblay L, Monette J. An outbreak of scabies in a long-term care facility: the role of misdiagnosis and the costs associated with control. Infect Control Hosp Epidemiol 2006: **27** (5): 517–518.
109. Burkhart CN, Burkhart CG. Before using ivermectin therapy for scabies. Pediatr Dermatol 1999: **16** (6): 478–479.
110. Chambliss ML. Treating asymptomatic bodily contacts of patients with scabies. Arch Fam Med 2000: **9** (5): 473–474.
111. Elston DM. Controversies concerning the treatment of lice and scabies. J Am Acad Dermatol 2002: **46** (5): 794–796.
112. Sargent SJ, Martin JT. Scabies outbreak in a day-care center. Pediatrics 1994: **94** (6 Pt 2): 1012–1013.
113. Flinders DC, De Schweinitz P. Pediculosis and scabies. Am Fam Physician 2004: **69** (2): 341–348.
114. Estes SA, Arlian L. Survival of *Sarcoptes scabiei*. J Am Acad Dermatol 1981: **5** (3): 343.
115. Aubin F, Humbert P. Ivermectin for crusted (Norwegian) scabies. N Engl J Med 1995: **332** (9): 612.
116. Meinking TL, Taplin D, Hermida JL, Pardo R, Kerdel FA. The treatment of scabies with ivermectin. N Engl J Med 1995: **333** (1): 26–30.
117. Meinking TL. Infestations. Curr Probl Dermatol 1999: **11**: 80–103.
118. Mytton OT, McGready R, Lee SJ, et al. Safety of benzyl benzoate lotion and permethrin in pregnancy: a retrospective matched cohort study. BJOG 2007: **114** (5): 582–587.
119. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. Lancet 1997: **349** (9059): 1144–1145.
120. Hernandez-Perez E. Resistance to antiscabietic drugs. J Am Acad Dermatol 1983: **8** (1): 121–123.
121. Currie BJ, Harumal P, McKinnon M, Walton SF. First documentation of in vivo and in vitro ivermectin resistance in *Sarcoptes scabiei*. Clin Infect Dis 2004: **39** (1): e8–e12. Epub June 11, 2004.
122. Marty P, Gari-Toussaint M, Le-Fichoux Y, Gaxotte P. Efficacy of ivermectin in the treatment of an epidemic of sarcoptic scabies. Ann Trop Med Parasitol 1994: **88**: 453.