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Luis Shimose & L. Silvia Munoz-Price

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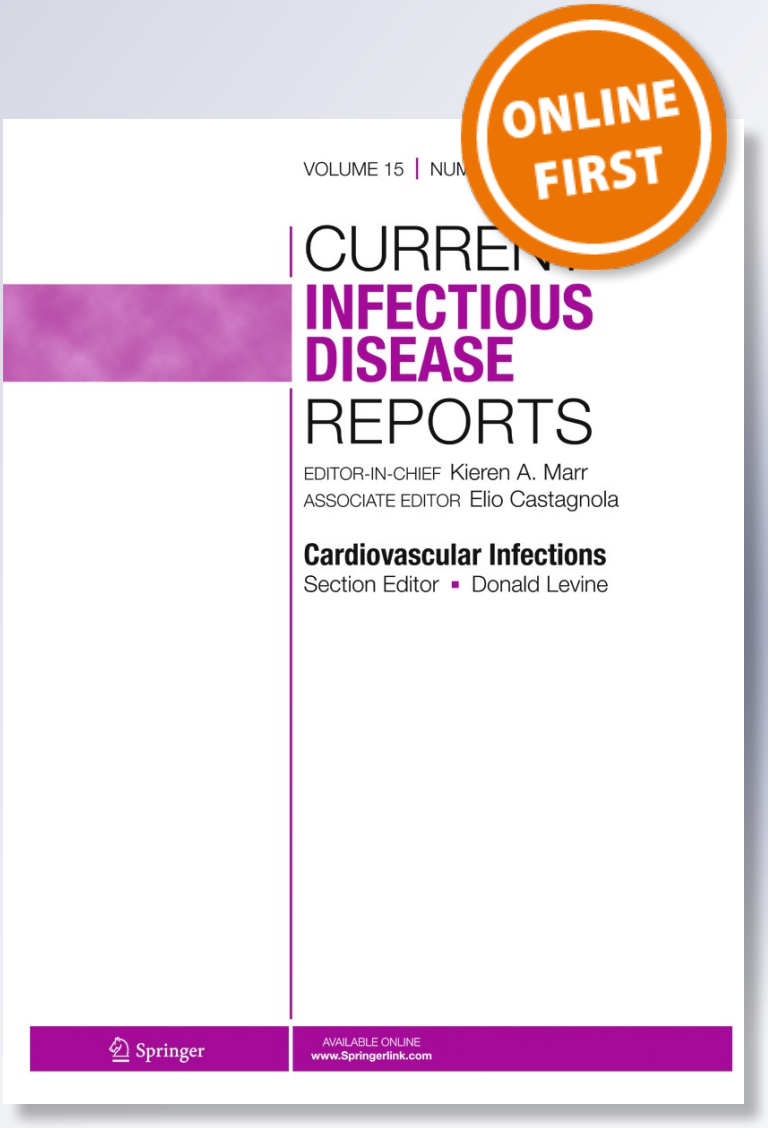

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Abstract Scabies remains a public health problem, especially in developing countries, with a worldwide incidence of approximately 300 million cases each year. Prolonged skin-to-skin contact is necessary to allow the transmission of the causative mite, *Sarcoptes scabiei*. Classic scabies presents with burrows, erythematous papules, and generalized pruritus. Clinical variants include nodular scabies and crusted scabies, also called Norwegian scabies. The diagnosis is based mainly on history and physical examination, but definitive diagnosis depends on direct visualization of the mites under microscopy. Alternative diagnostic methods include the burrow ink test, video-dermatoscopy, newly serologic tests like PCR/ELISA, and specific IgE directed toward major mite components. Treatment of scabies consists of either topical permethrin or oral ivermectin, although the optimal regimen is still unclear.

Keywords *Sarcoptes scabiei* · Scabies · Diagnosis · Video-dermatoscopy · Treatment · Topical · Oral · Permethrin · Ivermectin · Lindane · Crotamiton · Malation

L. Shimose · L. S. Munoz-Price
Department of Medicine, University of Miami, Miami, FL, USA

L. S. Munoz-Price
Department of Anesthesiology, University of Miami, Miami, FL, USA

L. S. Munoz-Price
Department of Public Health Sciences, University of Miami, Miami, FL, USA

L. Shimose · L. S. Munoz-Price
Jackson Memorial Hospital, Miami, FL, USA

L. S. Munoz-Price (✉)
Park Plaza West L-302, 1611 N.W. 12th Avenue, Miami, FL 33136-1096, USA
e-mail: smunozprice@med.miami.edu

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Introduction

Scabies is an ectoparasitic infestation caused by the mite *Sarcoptes scabiei* variety hominis, an arthropod of the order Acarina [1]. The name *Sarcoptes* is derived from the Greek word *sarx*, meaning *flesh*, and the word *koptein*, which means *to smite* or *to cut*. *Scabiei* comes from the Latin word *scabere*, which means *to scratch*. Aristotle was the first one to use the word *Akari*, although this was not *S. scabiei* but a mite living in the woods [2]. *S. scabiei* was first described more than 2,500 years ago, but it was not until 1687 that the causative organism was identified by Bonomo and Cestoni using a light microscope [2].

The aim of this article is to review the latest scientific articles on the diagnosis, prevention, and treatment of scabies. Additionally, we provide a summary of the epidemiology and clinical manifestations of the disease.

Epidemiology

Scabies occurs worldwide and is considered a significant public health problem, especially in the developing world [3], with an incidence of 300 million cases each year [4]. It predominantly affects children living in poor and overcrowded tropical areas [3]. This preferential distribution among younger populations is believed to reflect both increased exposure to the parasite and lack of immunity of the host. Scabies affects genders equally, and its ethnic differences are most likely related to variables such as overcrowded housing and socioeconomic and behavioral factors, rather than racial variables alone. Other risk factors include poverty, poor nutritional status, homelessness, dementia, and poor hygiene [5, 6]. Outbreaks frequently occur in institutions such as hospitals, nursing homes, prisons, and kindergarten classrooms. In 2012, Chun-Hao et al. showed that patients who were bedridden or were living in nursing homes, patients who had a higher

clinical severity status before admission, or patients who had a catheter inserted (including nasogastric, urinary, or intravascular catheters) were significantly more likely to acquire scabies while institutionalized [7].

The transmission of scabies occurs when newly mated female mites penetrate the skin into the epidermis. This is thought to be caused by the secretion of a solution that dissolves the host's skin, rather than digging or tearing their way into the host [8]. These fertilized adult female mites burrow into the stratum corneum. Once there, they lay eggs at an average of 0–4 eggs per day for up to 2 months. However, fewer than 10 % of theses eggs will develop into mature mites. The entire developmental life cycle from egg to adult spans approximately 2 weeks. Once the mites have reached the adult stage, they leave their burrows and emerge onto the skin surface, where they mate, thus repeating the life cycle. Male mites do not form burrows but, rather, stay on the skin surface, seeking new females to mate with, and die after mating. The average number of mites in an infected host is usually around 10 to 12; this relatively low number of mites might be explained as being due to mechanical removal of the mites by scratching, as well as the host immune response [1].

The most common source of transmission of scabies is prolonged skin-to-skin contact with an infested individual. Mites cannot fly or jump but, rather, crawl at an approximate rate of 2.5 cm per minute on warm skin [3–8]. Thus, it takes 15–20 min of close contact for successful direct transmission. Furthermore, mites can survive for 24–36 h at room temperature with average humidity [8]. Studies done by K. Mellanby showed that only two new cases of scabies (1 %) resulted from 63 experiments using underwear and blankets from heavily infested patients [9]. Moreover, none of the 25 experiments using blankets alone resulted in transmission of scabies [9].

The skin findings are the result of reactions to the mites, their saliva, eggs, and excrements. Findings include papules and pruritus caused by delayed type IV hypersensitivity reaction. Therefore, symptoms usually occur up to 4 weeks following the initial infestation. In cases of subsequent infestation, symptoms usually reappear more rapidly within a few days. Mellanby tried to reinfest patients who had previously been exposed to scabies [9]. He was successful in only 40 % of his subjects, indicating development of a certain degree of protective immunity [9].

Clinical manifestations as either classic or crusted scabies are a result of the type and magnitude of innate, cellular, and humoral immune responses to mite antigens. Current data suggest that in classic scabies, the protective immune response is dominated by a Th1 type cytokine response associated with CD4+ T-lymphocytes [10, 11•, 12]. On the other hand, in crusted scabies, the immune response was dominated by Th2 cytokines with CD8+ lymphocytes, which is nonprotective [10, 11•, 12].

Clinical Manifestations

The pathognomonic signs of scabies are burrows, erythematous papules, and generalized pruritus with nocturnal predominance; pruritus can also be present in unaffected skin. Burrows are serpinginous whitish lines in the outer epidermis of several millimeters in length [1]. Classic locations of burrows are the interdigital spaces of the hand, the flexural surface of the wrists, elbows, genitalia, axillae, umbilicus, belt line, nipples, buttocks, and penis shaft [1–3]. Additionally, secondary papules, pustules, vesicles, and excoriations are usually found. Among the pediatric population, scabies can also affect the head, neck, face, palms, and soles [3].

Nodular Scabies

Nodular scabies is a clinical variant occurring in about 7 % of cases. In this variant, extremely pruritic nodules 2–20 mm in size are present on the genitalia, buttocks, groin, and axillary regions. Nodules are reddish to brown, and because they do not contain mites, they are thought to be secondary to intense hypersensitivity reactions to mite products [13].

Crusted Scabies

Crusted scabies is also known as Norwegian scabies and was originally described by Danielson and Bock in 1848 among patients with leprosy [14]. Currently, most cases of this variant develop in patients with HIV or HTLV-1 infection or following immunosuppression after chemotherapy or organ transplantation [15]. Crusted scabies also has been described in patients with Down syndrome [13]. Approximately 40 % of cases with crusted scabies lack an identifiable risk factor, suggesting an inherited predisposition to this variant [15]. Crusted scabies presents as psoriasiform dermatitis with an acral distribution and variable whitish scaling. It usually involves the subungual area with extensive hyperkeratosis leading to nail thickening and dystrophy [1]. Crusted scabies carries a high mortality rate due to secondary sepsis [6] and, historically, has a 5-year mortality rate of up to 50 % [15].

Diagnosis

The diagnosis of scabies rests mainly on the history and physical examination, as well as the history of concurrent infection among household members and close contacts. A presumptive diagnosis can be made on the basis of the history of nocturnal pruritus and a typical distribution of the skin lesions [1], although scabies is easily mistaken for other pruritic skin conditions. The differential diagnosis is

long and includes atopic dermatitis, contact dermatitis, lichen planus, and papular urticaria, among others.

Microscopy

Definitive diagnosis relies on the identification of mites, eggs, eggshell fragments, or mite pellets. It is recommended to get multiple superficial skin samples from characteristic lesions—specifically, from burrows or papules and vesicles at the end of burrows. Lesions should be scraped laterally across the skin with a blade, ideally using oil, which helps the scraped material to adhere to the blade. The specimen should be examined under a light microscope on low power. Potassium hydroxide dissolves the keratin and provides clear visualization of the mites and eggs but may dissolve the mite pellets. The latter may be better visualized using saline or mineral oil [17]. Since an average of 10–12 female mites live on a host infested with classic scabies, failure to find mites is common and does not rule out scabies.

An alternative method to microscopy is the burrow ink test. With this method, the burrows absorb the ink and are readily apparent to sight [17]. Video-dermatoscopy with magnifications of up to 600 times is especially suitable for making the diagnosis of scabies in atypical cases, like the ones seen among the pediatric population [18]. One study showed that the diagnostic accuracy of the skin scraping technique could be increased when combined with dermatoscopy, especially in patients in whom steroids had been used previously [19•]. A 2011 systematic review of diagnostic methods for scabies found a positive likelihood ratio using dermatoscopy of 6.5 and a negative likelihood ratio of 0.1, when compared with skin scraping [20]. Dermatoscopy can also be used to monitor efficacy of treatment and optimal timing of the application of topical drugs [21, 22].

Even with all these diagnostic techniques, diagnosis of scabies is still challenging. A new approach for diagnosis of scabies is serologic testing. One study used polymerase chain reaction followed by ELISA to detect *S. scabiei* DNA from cutaneous scales in an infected patient [23•]. This same test became negative 2 weeks after treatment, indicating that this test can be used to monitor efficacy of therapy [23•]. In 2011, Rama and colleagues developed a specific IgE antibody against a recombinant scabies antigen. In this study, the sensitivity and specificity for diagnosing scabies were 100 % and 93.75 %, respectively [24••].

In a report from a region with a prevalence of scabies of approximately 13 %, the presence of diffuse itching, visible lesions in at least two typical locations, or a household member with itching had 100 % sensitivity and 97 % specificity for the diagnosis of scabies [25]. Such data are currently lacking from areas with lower prevalence of scabies [25].

Treatment

The cornerstone of treatment is to manage infested patients and all their close contacts concomitantly, regardless of the presence of symptoms.

Topical Agents

Permethrin and lindane are the two most studied topical agents for scabies. Permethrin is a synthetic pyrethroid compound applied as a topical 5 % cream. It works by disrupting the function of the voltage-gated sodium channels of the arthropods, causing prolonged depolarization of nerve cell membranes, thus stopping neurotransmission [26]. Permethrin is selective to invertebrates, due to the structural uniqueness of their voltage-gated sodium channels [26]. Lindane is an organochloride compound that causes neuronal hyperstimulation, leading to parasite paralysis [27]. There have been reports of neurotoxicity with this medication, which led to its removal from the market in several countries [28]. Another topical agent for the treatment of scabies is crotamiton, whose antiparasitic mechanism of action is still unknown. This drug has both antipruritic and antibacterial actions [28]. A 2010 Cochrane review on the treatment of scabies concluded that permethrin was more effective than either lindane or crotamiton [30••].

Ivermectin

An alternative approach to topical treatment is the use of oral ivermectin. Ivermectin works by activating a class of ligand-gated chloride ion channels, causing persistent depolarization [29]. This interaction is well studied in nematodes, and its targets include both GABA and glutamate-gated channels [29]. However, the target of this drug in *S. scabiei* has not been identified yet [26].

Ivermectin Versus Permethrin

In 2000, Usha et al. compared the efficacy of oral ivermectin versus topical permethrin, showing that a single dose of ivermectin was less effective than topical permethrin, with a cure rate of 70 % versus 98 %, respectively. In the same trial, when a second dose of ivermectin was administered to patients who did not respond to the first dose, the cure rate increased to 95 % [31]. This lack of efficacy of a single dose of ivermectin may be due to lack of ovicidal effect of the drug. The latter is thought to be due to the immaturity of the mite's central nervous system, which is the target organ of ivermectin [31].

In 2011, Singal and colleagues evaluated the efficacy of topical 5 % permethrin, as compared with oral ivermectin, at a dose of 200 ug/kg/dose (used in either a single-dose or double-

dose regimen in a 2-week interval). At the end of 4 weeks, the cure rates in all three treatment groups were equally efficacious [32•]. In 2012, Goldust and collaborators also compared topical permethrin and oral ivermectin. At 2 weeks of follow-up, clinical improvement of both groups was similar [33••].

Ivermectin Versus Lindane

In 2013, Mohebbipour et al. compared oral ivermectin and topical lindane. This trial included 148 patients randomized to receive either ivermectin 200 ug/kg/dose or two applications of 1 % lindane at a 1-week interval. At 2 weeks of follow-up, single-dose ivermectin was as effective as two applications of lindane, but when a second dose of ivermectin was given, the resolution of symptoms was superior than using lindane alone [34••].

Ivermectin Versus Other Topical Agents

In a more recent trial published in 2013, Goldust and colleagues compared oral ivermectin with crotamiton 10 % cream (applied twice a day for 5 days) [35••]. A total of 320 patients were included and were followed up for a total of 4 weeks. A single dose of ivermectin was as effective as crotamiton, although a two-dose regimen of ivermectin was superior [35••].

More recently, ivermectin has been used as a topical agent. In 2013, Goldust et al. compared topical ivermectin with topical malation. In this trial, a total of 340 patients were randomized to receive either 1 % topical ivermectin or 0.5 % topical malation twice within a single week. At weeks 2 and 4, topical ivermectin was as effective as malation [36••].

Most experts recommend the use of 5 % permethrin as the first line of treatment for classic scabies. It should be applied to the entire surface of the skin, sparing the area above the neck. To maximize exposure to the mites and absorption of the drug, it is recommended to apply permethrin in the evening and leave it on overnight. A second application is usually indicated 1–2 weeks after the first application. An alternative regimen is oral ivermectin at a dose of 200 μg per kilogram of body weight. Ideally, ivermectin should be given with food in order to increase absorption and bioavailability of the drug. As was stated before, ivermectin does not have ovicidal activity, so a second dose should be given 1–2 weeks after initial treatment [13].

Complications

In many countries, complications from scabies are related to sleep loss due to intense pruritus, whereas in developing countries, secondary infections are the main problems. The best documented complication with scabies is superinfection caused by *Staphylococcus aureus* and *group A Streptococcus*. The latter can lead to glomerulonephritis and rheumatic fever [37]. In a study done in the Solomon Islands (25 % prevalence of scabies), 86 % of the scabies cases were colonized by streptococci, and 71 % of the latter was Group A streptococci [38]. This same study showed that control of scabies with ivermectin was associated with a significant reduction in both hematuria and isolation of streptococci from skin lesions [38]. The relationship between secondary skin streptococcal infection in scabies and rheumatic fever has been proposed on the basis of the geographical association of a high prevalence of rheumatic fever and a higher incidence of skin streptococcal infection [39]. Another infectious complication from scabies has been reported in Gambia where septicemia caused by *S. aureus* has been associated in infants with skin rash and possible scabies. There is also an isolated report of Gram-negative bacteremia in a patient with crusted scabies and HIV infection [16].

Prevention

As was mentioned earlier, the cornerstone of the management of scabies is treatment of all close contacts, including sexual contacts, even if asymptomatic. Identification and treatment of core transmitters with crusted scabies is also important, since this variety of scabies is very easily transmitted due to high loads of parasites. Therefore, treatment of contacts that have been even minimally exposed to patients infested with scabies is warranted.

Even though transmission from bed linens, furniture, and fomites is uncommon; clothes and bed linens should either be kept in a plastic bag for 72 h (since mites die within this period of time when they are separated from the human host) or machine washed at >50 C [40] and dried the day after its first treatment. Insecticides are generally reserved for material that cannot be laundered [40].

Mass drug administration offers an alternative approach to population control of scabies. Studies in endemic areas of scabies (e.g., Panama and northern Australia) have shown that mass treatment with topical permethrin can substantially reduce the prevalence of scabies and, also, reduce the number of cases of impetigo [41]. Oral ivermectin has also been used for mass treatment in the Solomon Island [38]; following this intervention, there was a significant reduction of scabies from 25 % to 1 %, with concomitant decrease of impetigo and hematuria [38].

Conclusions

Scabies still remains a significant public health problem, especially in the developing world. Diagnosis of the disease is still challenging. Efforts should be made to develop a standardized, reliable, and cheap method for the diagnosis of scabies that can

be affordable to underdeveloped countries, where most of the cases of scabies are seen. The ideal treatment modality is still unclear, and further research on this topic is warranted.

Compliance with Ethics Guidelines

Conflict of Interest Luis Shimose declare that he has no conflict of interest.

Silvia Munoz-Price declare that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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