Review Article:

Scabies,how difficult to treat- A systematic review

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Abstract

Background: Scabies is a neglected tropical disease that continues to have global impacts and long-term health consequences in all nations regardless ofsocial and economic status.Treatment failure is an important factor concerning the increase in scabies incidence over the last decade. Here, we present an updatedreview of scabies by focusing on the challenges and difficulties in treatment that prevent the efforts foradequate control of the disease. **Methods:**The Cochrane Database of Systematic Reviews, MEDLINE, SCOPUS, Google Scholar, PubMed, and MEDLINE were all used in a systematic search. We incorporated case-control studies, prospective or retrospective cohorts, randomized and quasi-randomized trials, longitudinal (one-arm) observational studies, and case series that were published in the previous ten years. Our search terms included "vaccine," "mass drug administration," "scabies," "Sarcoptes scabiei var. hominis," "treatment," "management," "research updates," and "outcomes." Studies that discussed treatment resistance, failure, and difficulties in treating scabies were included. To gather information on global scabies control initiatives, obstacles, and experiences, as well as knowledge gaps, needs assessments, and recommendations for the future, a literature search was conducted. The papers that were included were only published in English. **Results:** For the systematic review, a total of 26 studies met the eligibility requirements. Drug resistance, application errors (especially with topical agents), neglecting repeated treatments, insufficient compliance, reinfestation due to insufficient decontamination of the patient's environment, failing to treat contacts concurrently, and not providing written information about necessary measures are among the established reasons why treating scabies can be challenging. **Conclusion:** Scabies is a highly contagious parasitic cutaneous disease that is stigmatizing and debilitating. Increased awareness, accurate diagnosis, prompt treatment, and selecting the right treatment options are essential for the effectivecontrol of scabies and for the prevention of the spread of the disease. **Abbreviation:** NTD, MDT, IACS

Key words: Scabies, treatment, failure, challenges.

Introduction

Scabies affects 200 million individuals worldwide, according to estimates. In 2017, scabies was added to the list of tropical illnesses that the World Health Organization considers to be among the most neglected in the world, indicating the need for more comprehensive research to determine the disease burden and for widespread disease control measures[1]. The origin of this extremely contagious skin infection is the Sarcoptes scabiei (S scabiei) var. hominis mite, a restricted ectoparasite that resides in the epidermis and manifests as generalized pruritus.[2-4] Greek words "sarx" (which means "flesh") and "koptein" (which means "to smite or to cut") are the source of the name "Sarcoptes". The Latin verb "scabere," which means "to scratch," is the source of the name "Scabiei."[5] The mites that cause scabies can spread both directly and indirectly, affecting multiple family members simultaneously.[6] It is also recognized

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that scabies is a sexually transmitted infection.[7] The risk of scabies transmission is increased by the length and frequency of direct skin-to-skin contact, as well as by the amount of mites on the skin.[8] Effectively treating the patient and taking all necessary precautions to prevent the disease from spreading to other people are the main objectives of scabies therapy.

Up to 30% of cases may result in treatment failure, which is thought to be a significant contributing cause to the rising scabies incidence that has lately been documented in affluent nations.[9-12] It has been proposed that factors such as drug resistance, treatment choice, exposure to future transmission events, and host immunological condition are predictors of treatment failure.[13,14] Studies, however, have not undergone a systematic evaluation and are quite varied. The frequency of scabies that is resistant to therapy for different medications is also poorly documented. Moreover, a thorough analysis of the variables linked to treatment failure has not been done. To ascertain the challenges associated with treating scabies, we therefore carried out a comprehensive evaluation of observational studies and randomized clinical trials.

The goal of this article is to provide an overview of the difficulties in managing the illness with the resources at hand and stopping its spread.

Method

Search strategy:Five electronic databases—PubMed, Google Scholar, Cochrane Database of Systematic Reviews, MEDLINE, and SCOPUS—were thoroughly searched. The pertinent studies that have been published in the past 10 years have been chosen. We measured at least one of our outcomes of interest (i.e., treatment failure, reinfestation, retreatment/recurrence, persistent itching, susceptibility to scabies mites, or risk factors for treatment failure) using randomized and quasi-randomized trials, prospective or retrospective cohorts, case-control studies, longitudinal (one-arm) observational studies, and case series. The original search plan was developed on PubMed and subsequently modified to fit the included databases' formats. To incorporate the various keywords into the search method, the Boolean operators "OR" and "AND" were employed.Articles resulting from these searches and relevant references cited in those articles were reviewed. The most relevant articles were included in this review. Keywords in our search included “scabies”, “Sarcoptes scabiei var. hominis”, “treatment”, “management”, “research updates”, “mass drug administration”, “vaccine” “challenges” and“outcomes”.

Inclusion and exclusion criteria:Only human studies were eligible for inclusion. A literature search yielded 196 initial hits; after screening following the defined inclusion and exclusion criteria, 26 studies were selected for this review. Finalinclusion was subjectively restricted to 26major medical and epidemiological articles basedon their relevance to the study objectives and aims. A systematic literature searchwas performed givingpreference to review articles, large epidemiologicalfield studies, and articles that comprehensively and/orappropriately covered the topics of interest and helpedexplain the significance of the issues this article covers. Studies that discussed treatment resistance, failure, and difficulties in treating scabies were included. The papers that were included were only published in English.

Articles that only discussed scabies guidelines or protocols in a specific nation or institution, or that presented a case study of a single patient or an outbreak of scabies in a single institution, were also disqualified. Excluded from consideration were any research that listed scabies among a variety of illnesses, indications, causes, or coexisting conditions. To find any manuscripts that the search strategy missed, reviewers' reference lists were examined.

Data extraction: The literature search aimed to retrieve information on control efforts, challenges, experiences, knowledge gaps, and needs assessments and recommendations for the futurein the field of global scabies control. We intended to compile data from multiple articles regarding the same study to ensure complete data extraction. The identified papers were first searched for duplicates then the remaining papers had their titles screened to allow for the quick elimination of studies that did not fit the inclusion Criteria.All titles and abstracts identified were screened for relevance and resolved the queries. Then full texts of papers assessed to be relevant were reviewed.

Quality assessment: We used the Cochrane Collaboration’s tool for assessing the risk of bias. Studies were assessed independently by two investigators in multiple domains of bias, including selection, performance, detection, attrition, and reporting. We also assessed the response or participation rate in the study, the quality of the scabies assessment (as described in the study report), and the statistical analysis of the results.

Compliance with Ethics Guidelines

This article does not include any research that we have done using humans or animals; instead, it is based on earlier investigations.

Scabies epidemiology: According to the most recent estimates, 150–200 persons worldwide contract scabies annually, with Asia, Oceania, and Latin America having the highest rates of scabies cases15. Young children who live in crowded conditions in impoverished populations are more frequently at risk16. Since scabies is contagious, people who live with patients may often become infected. There is an increased risk of scabies and associated breakouts for those who live in crowded housing situations or in clustered communities. Scabies is endemic in areas with few resources, where poverty and overcrowding are more prevalent. The mite can spread widely in households where there is inadequate access to treatment and high population density. When people who reside in these endemic areas seek treatment, they frequently return to rapid re-infestation.[17]

Scabies mites

Sarcoptes scabiei var hominis, an obligate human parasite,is a member of the family Sarcoptidae, which belongsto the order Astigmata, in thesubclass Acari, class Arachnida.The parasite is white-brownin colour and has 4 pairs of legs.The size of female mites is roughly double that of male mites, measuring 0.3 × 0.4 mm.[18] Male mites that land on human skin look for unfertilized female mites, mate on the skin's surface, and promptly perish after mating.[19-21] With their powerful mandibles, fertilized female mites excavate tunnel-like burrows in the stratum corneum. The release of proteolytic enzymes, which break down the stratum corneum, speeds up this process, which typically takes 20 to 30 minutes.[19-21] They keep on burrowing at a rate of 0.5 to 5mm per day for the rest of their life which is approximately 4to 8 weeks.[19-21] Fertilized female mites lay 0 to 4 eggs perday for an average of 40 to 50 eggs during theirlifetime.[20,21] The eggs are deposited in the burrowed tunnel andhatch in 2 to 5 days19. The larvae burrow into the intactstratum corneum tomake short borrows where they molt intonymphs, mature into adults in 10 to 17 days, and emergeonto the skin surface.[20] Mites can crawl at a rate of 2.5 cm/minute onwarm skin but are unable to jump or fly[19,20] At normal room temperature and with a relativehumidity of 40 to 80%, scabies mites can survive outsidethe human body for 24 to 36 hours.[22] Scabies mites are resistant to alcohol and soap23. On average, fewer than 10% of the eggs will develop intoadult mites.[20] With classicscabies, the average burden on anormal host is 10 to 15 live adult mites at any given time.[19,22] In temperate climates, the incidenceis higher in fall and winter than in summer.[19] Predisposingfactors include poorhygiene, malnutrition, poverty,overcrowding, homelessness, reduced access to healthcare, indiscriminate sexual contact, dementia, poor sensoryperception, and immunodeficiency. Community-wide outbreaks have occurred inhospitals, child-care settings, nursing care homes, and long-term care facilities.[24] Scabies is common in developingcountries.[25] The risk of transmission increases with the durationand frequency of direct skin-to-skin contact as well asthe number of scabies mites on the skin.[21]

Scabies diagnosis

The International Alliance for the Control of Scabies (IACS) was founded in 2012, and its members produced scabies diagnosis criteria in 2018 and 2020, respectively. In a Delphi consensus survey, a group of 34 international experts originally developed the IACS criteria.[26] Three levels of certainty were suggested for the diagnosis: clinical, confirmed, or suspected scabies.

The 2020 International Alliance for the Control of Scabies (IACS) has summarized its diagnostic criteria for scabies.[27]

A: Confirmed Scabies

A1: Mites, eggs, or faeces on light microscopy of skin samples

A2: Mites, eggs, or faeces on the individual using a high-powered imaging device

A3: Mite visualized on the individual using dermoscopy

B: Clinical Scabies

B1: Scabies burrows

B2: Typical lesions affecting male genitalia

B3: Typical lesions in a typical distribution and two history features

C: Suspected Scabies

C1: Typical lesions in a typical distribution and one history feature

C2: Atypical lesions or atypical distribution and two history features

H: History Features
H1: Pruritus
H2: Close contact with an individual who has had itch or typical lesions in a typical distribution.

The diagnostic criteria have limitations in that it does not include the diagnosis of variant or atypical presentations of scabies, such as bullous scabies, crusted scabies, scabies in immunocompromised individuals, or scabies in the elderly, intellectually disabled, or bedridden individuals. Consequently, clinical judgment remains imperative in the diagnosis of scabies. There are currently no easily accessible laboratory tests to confirm scabies. Rather, the "gold standard" is to use a microscope to see mites, eggs, or feces. The justification for a novel, trustworthy technique to diagnose scabies is supported by the fact that microscopy detection rates range from 10 to 70%.[28] The need for intrusive skin scrapings has been eliminated by dermatoscopes, however, dermoscopy still requires an operator. Dermatoscopes arenot affordable in all regions, cannot visualize feces or eggs, and are harder to detect mites in darker skin types.[27]

Treatment of scabies

For scabies, several approved therapies exist. There are topical (such as lindane, permethrin, sulfur-containing treatments, crotamiton, malathion, and benzyl benzoate) as well as oral (such as ivermectin, thiabendazole, and flubendazole) remedies available. In several jurisdictions, oral ivermectin has not been authorized for the treatment of scabies, and it is not readily available. The standard treatments are topical and usually need to be applied all over the body for eight to twelve hours. After seven to fourteen days, a second application is advised. The ideal course of treatment is not universally agreed upon, and suggestions made in one country may not be suitable in another. To prevent infestation, every close personal contact of the patient should receive treatment at the same time. According to the 2017 European Guidelines for the Treatment of Scabies, topical therapy should be used on all skin areas including the skin beneath the ends of the nails.[29]
Itching is a common side effect following scabies treatment, and it can last for two to four weeks. Emollients should be applied often to relieve post-treatment itching. Oral antihistamines and low-dose topical corticosteroids may also be utilized in some circumstances.[29] Two weeks following the last scabicide treatment, a microscopic examination is advised to evaluate the efficacy of the treatment.[29] It can take up to six weeks following the end of treatment for symptoms and indicators of hypersensitivity to go away, thus it is best to wait until then to determine treatment failure.
To achieve treatment success, not only is ordering the proper scabicide needed, butthe washing of clothing, bedding, towels, and other items is needed; these items should bemachine washed (at least at 500C), drycleaned, or sealed and stored in a plastic bag for 1 week.[29]

Challenges related to therapy

It has been difficult to treat children since, for a long time, there was no clear protocol for treating scabies in children, and did not result in a full recovery.[30] As of right now, the guidelines specify which precise acaricides to use and at what doses for newborns and older children. Children as young as two months old are permitted to use permethrin. Children under the weight of 15 kg should not be administered ivermectin.[29] Because there was insufficient information on the adverse effects of the available acaricides, the treatment of pregnant women was also controversial for a long time. Permethrin, benzyl benzoate, and sulfur are suggested as safe therapeutic alternatives in pregnancy by the most recent treatment guidelines.[29]
Inadequate drug administration, length of treatment, wrong dosage, or drug resistance are among the possible causes of treatment failure for Sarcoptes, as reported in the literature. In multicenter research comprising 112 patients, Aussy et al. found that the reason for therapy failure was a single dose of ivermectin (as opposed to two intakes) and topical benzyl benzoate alone.[31] However, Sunderkötter et al. clarified that failing permethrin treatment could be brought on by insufficient exposure to this acaricide.[32] Additionally, Isogai et al. clarified that subungual debris and nails might harbour Sarcoptes mites and eggs.[33] Furthermore, the overall state of the patient (such as immunosuppression) may impact the course of therapy, necessitating the use of multiple acaricides or extending its duration.[34] Research has indicated that in impoverished areas, living in close quarters with high population density, having frequent physical contact, sharing clothes, bedding, and other items, and having inadequate shelter are the primary community-level risk factors for scabies infestation and severe infection.[39,40]

New Treatment Options for Scabies

New studies are being conducted because new scabicides are needed that are more effective against eggs and have a half-life that extends to the entire 14-day life cycle of the mite. Moxidectin is also being studied as an oral alternative to ivermectin. Ivermectin and moxidectin are members of the same family. It is noteworthy that this medication has a substantially longer half-life in plasma and the skin than ivermectin, as well as quick absorption and wide distribution37. Because of this pharmacological feature, it could be able to treat the scabies mite during its whole life cycle. In a preliminary study using an experimental pig model for scabies, a single oral dose of moxidectin proved to be more successful than the traditional two doses of ivermectin. In Australia and France, a multinational clinical phase II trial aims to develop moxidectin as a novel single-dose scabies treatment (NCT03905265).[43]

Higher doses of ivermectin are an intriguing alternative that is presently being researched for the treatment of scabies44. There's a growing theory that a greater ivermectin dosage might be required to treat the parasite infection. When this idea was first brought up concerning head lice infestation, research revealed that a twofold dose of 0.4 mg/kg ivermectin was roughly 95–100% effective45. The efficacy of ivermectin given orally as the higher double dose of 0.4 mg/kg with the conventional treatment dose of 0.2 mg/kg, given three times seven days apart (on D0, D7, and D14), is being compared in a randomized controlled clinical trial approved by the French Ministry of Health. Both arms are supplemented with daily application of emollient therapy and topical5% permethrin on D0 and D7 (GALECRUSTED, NCT02841215).[46]

The value of pets as "family members" has steadily increased in recent years. Studies in this regard have demonstrated the efficacy of treating fluralaner topically and orally. Chitin, a vital part of the exoskeleton of arthropods, including the scabies mite, is blocked from being synthesized by fluazuron. It does not work against adult mites; instead, it stops the development of new larvae inside the eggs. A single dose of the innovative medication fluralaner, which is safe, efficacious, and maintains results for twelve weeks after treatment, can be used to treat canine sarcoptic mange.[38]

Mass drug administration

Treatment for scabies is typically directed at the patient and their household contacts in nations where the disease is infrequent. It has been discovered that treating the entire population at once is more successful when scabies become endemic.[41] This is known as mass drug administration, and it can be applied nationally or in places where people are confined, such as jails, hospitals, nursing homes, and schools.[42] Oral, topical, or systemic medicine may be used in MDA.

Nevertheless, there is still debate regarding the use of oral ivermectin in MDA.[47] Firstly, there are some countries where the medicine is not approved for the treatment of scabies, and it has been connected to certain safety issues with pregnant women and children under the age of five.[47] Second, similar to topical medications, resistance may arise with protracted, recurrent regimens of oral ivermectin.[48,49] Third, there is evidence from certain studies that ivermectin does not work as well as topical agents.[50,51]

Vaccines

In endemic locations and for cases of crusted scabies, vaccinations are anticipated to be a viable means of preventing the development of scabies.[35] It is common for a second scabies infestation to be less severe than the first, and numerous accounts exist of animals developing immunity following a prior infestation. As a result, a vaccination might work. Recent advances in our understanding of the interplay between Sarcoptes and the immune system of the infected individual should have a positive impact on efforts to develop a vaccine. With increased host antibody levels and fewer mites after infection, immunity develops quickly.[36] Mice and rabbits were used in an animal model to test an anti-mite vaccine; nevertheless, more trials are required.

What actions are necessary to effectively control scabies?

Plans for further research and other requirements:

The literature on scabies still has a lot of significant gaps.[52] The initial areas of concern concerning therapy are safety and the limitations of the therapeutic choices that are now accessible. There are issues with ivermectin and other medications in young children and during pregnancy, and more research is needed on ivermectin dose optimization. The emergence of mite generations resistant to various scabicidal medications, the most effective treatment for crusted scabies, and the poor efficacy of current treatments in preventing relapses all require more research. The development of vaccines

is the last field still awaiting advancement. Guidelines for the best therapeutic approaches should also be developed to address consequences such as secondary bacterial infections, inflammatory skin reactions, and other issues.We should support comparative research to evaluate novel medications. To determine if MDA is a successful community-wide scabies control strategy, more research is required. Additional thought must be given to the economic impact of scabies to calculate its direct and indirect costs.[53] It is also necessary to map the prevalence of disease in neglected areas, such as impoverished populations in Africa.[54] Furthermore, financial agencies should refocus their efforts on scabies because it is a disease mostly affecting the impoverished. Financing for research on population-based tools, diagnostics, and therapy should be prioritized.

A hopeful start toward scabies control was made in 2020 when scabies was added to the new WHO roadmap for neglected tropical diseases 2021–2030, taking into account the needs previously mentioned.[55] Scabies control, not eradication, is the goal of this strategy. A measure of advancement towards the roadmap's scabies control objective will be the count of nations that have integrated scabies control into their universal health care program. It is anticipated that this indicator will rise from the baseline value of zero in 2020 to 25 (13%) in 2023, 50 (26%) in 2025, and 194 (100%) countries in 2030.The WHO states that the roadmap is intended to serve as a call to action for various nations, funders, policymakers, researchers, and disease experts to work together and connect their plans and strategies to create coordinated efforts toward the control and eradication of NTDs, and consequently lessen the suffering of impoverished populations affected by them. It is believed that drawing attention to scabies in this manner will concern everyone worried about the urgent need to further investigate and coordinate activities aimed at eradicating this illness.

Conclusion

Standardizing treatment guidelines for scabies is one of the measures that have been used. In endemic areas, mass drug administration is a campaign intended for both prevention and treatment. The present medications used to treat scabies are unfortunately not working as well as they once did, thus new treatments must be found. New acaricides are being created for this reason to improve therapeutic choices that will benefit the patient and successfully treat this illness. Additionally, prevention is required before contracting scabies, particularly for those residing in endemic areas. Regretfully, efforts to develop a vaccination that works have not yet been successful. Drug resistance, mistakes made when applying medication (especially topical treatments), missing follow-up treatments, low compliance, reinfestation due to insufficient environment decontamination, treating contacts at the same time, and not providing written instructions about necessary precautions are all known reasons why treating scabies can be challenging.

Controlling scabies worldwide is now possible, despite the present obstacles. Scabies global control appears to be a worthwhile, realistic goal that may be accomplished in the not-too-distant future with persistent interventions, ongoing resources, genuine commitment and support, and a focus on the targets and indicators identified in the WHO roadmap for NTD 2021–2030.

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Conflict of interest

The authors declare no conflict of interest, financial orotherwise.

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