Treatment and control of scabies

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Purpose of review
The treatment of individual patients with scabies and its control in institutional and community settings remains challenging, with relatively few treatment choices available. In this review, evidence of the efficacy of available treatments will be discussed, and possible emerging drug resistance and new therapeutic directions outlined.

Recent findings
Although there has been attention on the use of ivermectin for the treatment of ordinary scabies and for mass drug administration, evidence supporting its superiority for both indications over alternative treatment is inconclusive. This is particularly true in light of several case reports of drug resistance in human and veterinary settings when the drug has been intensively used. When used correctly, topical agents such as permethrin and benzyl benzoate are effective. Little research on the development of new and more effective acaricides suitable for human use is underway. While the in-vitro acaricidal properties of several natural products have been documented, these are yet to be evaluated in animal studies or clinical trials.

Summary
When properly administered, chemotherapy for scabies remains effective in most situations. However, with reports of drug resistance increasing and with the need for therapies suitable for use in interventions to control community outbreaks, there is a need to develop new therapies.

Keywords
drug resistance, ivermectin, permethrin, scabies, treatment

INTRODUCTION

In the last decade there has been no significant improvement in the availability of treatment for scabies. Instead, there has been a growing body of evidence from clinical studies of the limitations of currently available treatments, as well as ongoing uncertainty regarding the safety of the available treatments. Likewise, the diagnosis of scabies almost universally relies on clinical judgement. In the most recent Cochrane review of treatments for scabies [1▪▪], updated in 2010, weaknesses in study design were highlighted, and the reviewers concluded that there was a paucity in high-quality data on the relative efficacy of available treatments for scabies. Here, we review recent developments in the area, with a focus on the years 2009–2012.

TREATMENT OPTIONS FOR SCABIES

Scabies treatment has typically entailed the application of a topical acaricide, although oral administration of ivermectin is being increasingly used. For all topical treatments, patients are advised to cover the entire body from the neck down and leave the cream on for a prolonged period (usually overnight), before washing off. In pediatric and geriatric patients, the face is also treated due to more generalized skin involvement in these groups. The treatment of contacts is emphasized to prevent possible reinfestation, as patients can remain asymptomatic for several weeks following infestation.

Topical acaricides include longstanding formulations, such as 8–10% sulphur, 10–25% benzyl benzoate, 1% lindane, 10% crotamiton, 5% permethrin, or 0.5% malathion. The choice depends on local availability, cost and practitioner preference.

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Curr Opin Infect Dis 2013, 26:133–139
DOI:10.1097/QCO.0b013e32835e1d57

KEY POINTS

- There is an imprecise understanding of the efficacy of available acaricides.
- Permethrin cream appears to be the most effective topical agent.
- Although benzoyl benzoate is highly effective, the recommended administration method is not supported by in-vitro data.
- Ivermectin is a treatment option, but available data indicate that two treatments are necessary to effect reliable cure. Defining its safety in young children and pregnancy remains a priority.
- There are a number of agents not currently used that would likely be effective. These include synergized pyrethroids, other macrocyclic lactones including moxidectin, and agents shown to be well tolerated for treatment of ectoparasites in companion animals and livestock.
- Well designed epidemiologic studies are a high priority to better understand transmission and control.

Permethrin

The synthetic pyrethroid 5% permethrin is a first-line acaricide in many countries, including the United States, Australia and the United Kingdom. It has an excellent record for safety and low toxicity. In a Cochrane review it was concluded that it was the most effective scabies treatment currently available [1▪▪]. Recent findings concur, with all studies reporting more than 90% 14 or 28 day cure (Table 1 [2–6,7▪,8▪]). While in many reports its effectiveness when applied as a single dose has been satisfactory [4,6,8▪], its efficacy as an ovicide remains unresolved, and therefore a second treatment after 1 week to kill residual hatched eggs is prudent. A significant limitation to more widespread use of permethrin is its cost, which is significantly higher than other topical treatments, and the fact that it is not available in some areas, especially in the developing world where the burden of scabies is likely higher [8▪]. In addition, there are suggestions of emerging resistance (see below).

Benzyl benzoate

Benzyl benzoate is used at a concentration of 25% in adults, and 10% or 12.5% in children. It advantages include: its high efficacy, especially at 25%; that no resistance has been reported; and its low cost. It is therefore a very popular treatment in Africa and parts of Europe, although it is not available in the United States. A limitation is that the drug is prone to cause significant immediate skin irritation, thereby limiting its tolerance; dilution to reduce this may reduce efficacy. For example, in a recent trial 17.6 and 37.5% of patients reported irritation with one or two doses of benzyl benzoate, respectively [7▪]. Treatment guidelines recommend that benzyl benzoate be left on for 24 hours and/or used on repeated consecutive days, an application regime that is more intensive than recommended for permethrin for example. The rationale for this recommendation is not clear, as compared to other commercially available acaricides, 25% benzyl benzoate is an extremely rapidly acting acaricide *in vitro*, with death of mites occurring within 30 min [9,10,11▪,12]. There is a paucity of studies comparing different treatment regimens for benzyl benzoate, with the exception of a study by Ly *et al.* [7▪], who reported that that the difference between one or two doses was modest (Table 1). Trials comparing the efficacy of short versus long application times would be beneficial, as reduction in application time could reduce adverse effects and increase acceptability of an otherwise effective and affordable drug.

Controversies over lindane

1% Lindane (γ benzene hexachloride), an organochloride insecticide and formerly the treatment mainstay, has been withdrawn from many regions worldwide due to concerns regarding neurotoxicity. In some countries however, it remains utilised as a first or second-line treatment [3,13,14]. Although some proponents have attributed adverse events (including ataxia, tremors, seizures) to inappropriate or excessive application, a recent review of lindane adverse events showed that 43% of serious adverse events occurred when the drug was used as labelled [15▪]. Due to the potential risks, these authors recommended that lindane be removed from other markets. The merit of continuing to recommend use of lindane is further weakened by evidence suggesting that it is less effective than available alternatives [1▪▪,3] (Table 1).

Other topical agents

Topical application of 8–10% precipitated sulphur, although effective, is rarely a popular choice due to its messy application and odour. It is still used in some areas due to its low cost and its wide margin of safety in infancy and in pregnant women. In a recent study, it was confirmed that application for three consecutive days was required for optimal efficacy (Table 1) [5]. Crotamiton, another old drug that has not been evaluated recently, when used at a

Table 1. Treatment trials for scabies, 2009–2012

Reference	Drug	Treatment regimen	*n*	Day 7 cure rate (%)	Day 14 cure rate (%)	Day 28 cure rate (%)
[2]	Permethrin	5%, topical, two applications, 1 week apart	121		92.5	
	Ivermectin	200 μg/kg, oral, single dose	121		85.9	
[3]	Permethrin	5%, topical, two applications, 1 week apart	110		83.6	96.3
	Lindane	1%, topical, two applications, one week apart	110		49	69.1
[4]	Permethrin	5%, topical, single dose	105	74.8	99	100
	Ivermectin	200 μg/kg, oral, single dose	105	30	63	99
		1%, topical, single dose, only to affected sites	105	69.3	100	100
[5]	Sulfur	8–10%, single dose	33			42.4
		8–10%, three consecutive days	32			96.9
		8–10%, three consecutive nights	32			90.6
[6]	Permethrin	5%, topical, single dose	40	67.5	86.8	94.7
	Ivermectin	200 μg/kg, oral, single dose	40	35	77.5	90
		200 μg/kg, oral, two doses 14 days apart	40	30	66.7	89.7
[7▪]	Benzyl benzoate	12.5%, topical, single dose[a]	68		54.4	76.5
		12.5%, topical, two doses, 1 day apart[a]	48		68.8	95.8
	Ivermectin	150–200 μg/kg, oral, single dose[a]	65		24.6	43.1
[8▪]	Benzyl benzoate	25%, topical, two doses on consecutive nights	35	76	92	
	Permethrin	5%, topical, single dose	34	82	96	
	Ivermectin	200 μg/kg, oral, single dose	34	56	100	

[a]Treatment failures at day 14 were given a second application of the drug.

concentration of 10% has a wide margin of safety and is suitable for infants. Although crotamiton has good acaricidal properties *in vitro* [10], clinical efficacy is variable, with multiple applications advised [1▪▪]. Nonetheless, it remains an option when responses to other acaricides are deemed inadequate. In addition, it may also be a good adjunct therapy due to its antipruritic activity.

Malathion is an organophosphate insecticide, reported to be effective for scabies at a concentration of 0.5% [16]. Although it is currently recommended as a second-line treatment in the United Kingdom, there is a paucity of published clinical trial data to support its use.

Oral ivermectin

Although the utility of ivermectin for the treatment of scabies is now widely recognized, its use remains off-label in most countries. It is most commonly administered at a weight-based dose of 200 μg/kg, although lower doses have been used in some trials [7▪]. The principal indication for oral ivermectin therapy has been for the treatment of the most severe form of infection, namely crusted scabies [17▪▪]. In addition, it has been used in mass treatment settings, and for control of institutional outbreaks in which topical application is less practical. The obvious advantage of an oral medication over topical therapy is that correct drug administration and compliance with treatment is more likely, not a trivial consideration. A disadvantage is that ivermectin is not approved for use in children below 15 kg, or in pregnant or lactating women. As these groups often carry a high burden of scabies in the community, this represents a significant obstacle to its use in mass treatment.

Despite early hopes that this drug would revolutionize the treatment of scabies, in a meta-analysis of published trials it was concluded that single dose ivermectin was not as effective as single-dose permethrin; the administration of a second dose of

ivermectin resulted in efficacy similar to permethrin [1▪▪]. In one recent trial in which two doses of permethrin were compared with a single dose of ivermectin, only a small and nonsignificant advantage was observed with permethrin (93 vs. 86%) [2]. These results are in contrast to other trials in which day 14 efficacy was reported to range from 26 to 100% [4,7▪,8▪] (Table 1). Chhaiya *et al.* [4] also examined topical application of 1% ivermectin, and found it to be more effective than a single dose of oral ivermectin. Strangely, the investigators advised patients to only apply the cream to affected sites, which goes against principles for the topical treatment of scabies. Thus, results should be interpreted with some caution.

It is important to recognize as a general comment that the contrasting outcomes reported in clinical trials likely reflect major differences in definition of cure. For some, this is defined as the absence of new lesions, whereas others require complete disappearance of all lesions [4,7▪]. In this respect, it is well recognized that the pruritus caused by scabies frequently persists for some time after the administration of curative therapy (see below).

Despite heterogeneity between trials, it is worth noting that several studies report slower responses to ivermectin compared with permethrin, with relatively lower cure at days 7 and 14, but increasing at day 28 (Table 1). Reasons for this difference are difficult to explain, but could relate to the rate of mite killing *in vivo*, the mechanism of action, or individual differences in the distribution and retention of ivermectin in skin and tissues [18▪]. The latter factor, although potentially of importance, has received little attention. Regardless, it is now generally accepted that single-dose ivermectin may be suboptimal due to its relatively short half-life in human plasma and its lack of ovicidal properties. Thus, some authors have recommended that a second dose 7 days later be administered.

GENERAL CONSIDERATIONS WHEN ASSESSING TREATMENT RESPONSE

An important factor that can confound assessment of treatment outcome is that the residual 'allergic' immune responses to mites can persist, or even increase, for weeks after mites have been killed. This persistence of pruritus, possibly resulting in further excoriation, is probably the single most important reason for perceived treatment failure, and can be a great source of frustration for patients. Thus, it is most important that this be clearly explained to the patient, and that they be advised that apart from symptomatic treatment they should avoid repeated application or ingestion of antiparasitic therapy, the former potentially exacerbating skin irritation. Treatment with antihistamines is a useful adjunct and may provide symptomatic relief during this 'mite clearance' period. Topical or oral corticosteroid therapy however should be used with caution due to the increased risk of masking treatment failure and predisposing to crusted scabies [19].

Treatment failures can be due to incorrect application of acaricide, reinfestation from untreated contacts, or mite resistance to acaricides. Although the third is commonly blamed and is of growing concern (see below), the first two scenarios probably account for the majority of reported treatment failures in scabies.

DRUG RESISTANCE IN SCABIES

As with most infectious diseases, the threat of emerging drug resistance in scabies is ever present. Although there is anecdotal evidence of resistance reported for most available acaricides, the fact that reports of treatment failure have not increased in frequency suggests that this problem is not yet widespread in scabies, compared to head lice for example. In the last decade, there have been two reports of the clinical treatment failure of ivermectin in scabies [20▪,21], with the former being confirmed by an in-vitro study of mites collected from patients with treatment failure. Examination of mite responses to ivermectin over the course of clinical treatment has demonstrated that selection for mites with increased tolerance to the drug occurs readily [9]. This study was undertaken in crusted scabies, in which mite populations are extreme and inadequate drug penetration of hyperkeratotic skin crusts by topical and parenteral acaricides may prevail. However, the results suggest that resistance may be readily selected with ivermectin. The finding that the transcription of a detoxification gene is rapidly upregulated in lice after sublethal exposure to ivermectin further supports the hypothesis that ivermectin resistance is inducible *in vivo* [22]. Where permethrin is concerned, resistance has been observed in an animal model of *Sarcoptes scabiei* var. *canis,* in which mites were exposed to permethrin for a prolonged period [23], but no cases in human scabies have been unequivocally documented. Laboratory studies indicate that acaricide resistance in scabies is likely mediated by P-glycoprotein mediated efflux (ivermectin) [24], sodium channel mutations (permethrin) [25], and increased activity of metabolic enzymes, such as esterases, cytochrome P450 and glutathione S-tranferases (permethrin and ivermectin) [11▪,24]. Of note, it has been shown that the addition of enzyme synergists to permethrin can reverse resistance *in vitro* [11▪], thereby suggesting a

path to improving topical therapy with pyrethroids by combining them with a synergist.

DEVELOPMENT OF NEW THERAPEUTICS FOR SCABIES

In the light of the suboptimal performance of available acaricides and with concerns regarding emerging resistance to conventional acaricides, the development of new therapeutic options is critical to the sustainable control of scabies. As noted above, a potential avenue to overcome resistance and improve efficacy may be the coformulation of pyrethroids with synergists, as is routinely undertaken in head lice products and domestic and agricultural insecticides. The use of synergized pyrethrins for scabies has been explored in one trial, with clinical efficacy equivalent to benzyl benzoate [26], the reference acaricide in many experimental settings. In this trial, the concentrations of both agents may not have been optimal for scabies (0.17% pyrethrin + 1.65% piperonyl butoxide versus 10% benzyl benzoate). Clinical trials measuring the efficacy of synergized versus conventional permethrin treatment would be of immediate interest. Similarly, P-glycoprotein inhibitors have been shown to restore sensitivity in ivermectin resistant nematodes [27].

Moxidectin is a macrocyclic lactone closely related to ivermectin but with the advantage of a much longer half-life (~4.5 days vs. ~18 h), which may offer potential to overcome the short half-life limitation of ivermectin thereby improving the efficacy of single dose therapy. Widely used in veterinary practice, it has recently been proven to be a well tolerated and effective acaricide against mange in goats and sheep [28,29]. Safety (phase I) studies of moxidectin in humans have recently been completed [30,31], including in breastfeeding women [32]. A phase II trial sponsored by the WHO has recently been completed where the efficacy of orally administered moxidectin in human participants with river blindness was evaluated (ClinicalTrials.gov Identifier: NCT00300768).

Along with moxidectin, other drugs approved for the treatment of mange in animals include amitraz, other synthetic pyrethroids, and fipronil (reviewed in [33]). Another interesting new class are the insect growth regulators (IGRs). These may offer potential of combination therapy with adulticidal acaricides, as they interfere with egg hatching and increase mortality when moulting. A recent study of one such IGR, fluazuron, on sarcoptic mange in pigs showed that although the cure rate was suboptimal, significant differences in population distribution and a reduction in larval stages occurred [34].

Two recent case reports document the successful treatment of crusted scabies with three doses of 800–1000 mg albendazole [35,36], although one of these studies included combined treatment with crotamiton and/or salicylic acid. As benzimidazoles are not recognized for activity against arthropods, preclinical investigations or animal model studies would appear to be appropriate before clinical trials are undertaken.

Alternative therapies and 'natural' products are often popular options, particularly among patients who become dissatisfied with treatment outcomes following prescribed or conventional acaricides. Several essential oils and herbal remedies show promising acaricidal activity *in vitro*. Recently described agents include eugenol and derivatives (clove oil) [12], *Azadirachta indica* (neem oil) [37] and *Eupatorium adenophorum* [38]. Tea tree oil (*Melaleuca alternifola*), is routinely used as an adjunct therapy for crusted scabies [17▪▪]. Very few of these natural products have been assessed for clinical efficacy or, more importantly, safety. In a preliminary study, Oyelami *et al.* [39], found that aloe vera had similar efficacy to benzyl benzoate, but numbers are too small to draw any conclusions. Despite contrasting clinical opinions on alternative therapies, a reality is that a large number of people use them, and will continue to use them, often in an ad-hoc and potentially hazardous way. It is therefore important that robust trials be designed and executed to provide better quality evidence for the therapeutic options for treatment scabies. In this respect, the Cochrane review [1▪▪] identified significant methodologic problems with most published trials, including randomization, allocation concealment, blinding and follow-up. A consensus recommendation regarding study design would be of assistance in guiding design of future studies. In addition to standard methodologic issues for trial design, critical parameters, including diagnosis, speed of response, and duration of follow-up should be agreed upon.

CONTROL OF SCABIES IN ENDEMIC POPULATIONS

As noted above, there is increasing recognition of the significant indirect morbidity that scabies causes, particularly group A streptococcal infection leading to postinfective sequelae, such as glomerulonephritis and rheumatic heart disease. Interventional studies have shown that community-based control of scabies can have major impact on these secondary effects [40▪▪,41]. In addition, the increasing deployment of so-called mass drug administration (MDA) for control of neglected tropical

diseases has led to efforts to control scabies using this approach [42]. In studies using topical permethrin [41,43▪] and oral ivermectin [40▪▪], significant success has been reported. MDA programs are most likely to succeed when a single dose of drug is highly efficacious, treatment coverage is high and the transmissibility of infection is not high. However, currently available therapies for scabies are suboptimal for this purpose. In addition, there is a paucity of reliable data on these parameters to determine the likely efficacy with available tools. Experience in the Northern Territory of Australia in indigenous communities indicates that there are significant difficulties in achieving sufficient coverage and sustainability using topical therapies, such as permethrin cream [44▪]. For ivermectin, the lack of safety data in small children and pregnancy has posed significant difficulties when community-control programs have been implemented [45], especially because these are major target groups in endemic populations. Permethrin cream, the most suitable topical treatment for community interventions, is expensive and not available in many endemic settings in the developing world. Ivermectin, while widely available and administered as part of programs to control onchocerciasis, is not readily available at affordable prices for scabies control. It is clear that in addition to the priority to optimize available treatments, it will be necessary to undertake well designed studies to define the optimum strategies to control scabies at community levels. It should also be stated that without overall economic improvement, especially in housing, any sustainable control of scabies would remain challenging.

CONCULSION

Although there are effective treatments available for therapy of individuals with scabies, there are many gaps in our knowledge about how to use currently available tools. In addition, the lack of a reliable diagnostic test makes management of scabies at both the individual and community level challenging. With the growing emphasis on so-called neglected tropical diseases and the availability of advanced laboratory techniques and knowledge of the appropriate epidemiologic approaches to gain better understanding of the burden of scabies, clinical trial design and modelling of likely intervention efficacy, there is the prospect of improving the inadequate situation of scabies control. In these times of competing health priorities and financial constraints it is important to recognize that scabies is much more than just an irritating skin condition, but one that leads to significant morbidity and a condition for which much could be done with readily available tools.

Acknowledgements

K.E.M. is supported by an Australian Research Council Discovery Early Career Researcher Award. J.S.M. is supported by a Queensland Health Clinical Research fellowship and National Health and Medical Research Council Practitioner Fellowship.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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