Katja Fischer
Olivier Chosidow *Editors*

Scabies

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Preface

Scabies mites are thought to have co-evolved with mammals, and they likely have plagued humankind since the very beginnings. The skin disease these parasites cause occurs everywhere around the globe, with tropical latitudes being disproportionately affected. Population density and poverty are the main drivers of scabies prevalence. Accelerated population growth in both rural and urban areas without corresponding improvements in the public health infrastructure, housing and sanitation causes increased prevalence of scabies. In addition, an increased trade, travel and population movement bring people from non-endemic areas into contact with the parasites.

Despite its wide distribution and its long history, this parasitosis has received little attention from science until recent years. Finally, in 2017 scabies disease was included into the WHO list of Neglected Tropical Diseases and a call for novel preventive strategies and treatments was voiced officially. This important milestone has prompted us to summarise and discuss the status quo of research into scabies disease at the start of the 2020s. We have recruited a large range of expert authors to accomplish this. Parts I and II cover basic biology research on the parasite. In Part III we address epidemiological aspects of scabies and in Part IV clinical manifestations and management.

We wish to thank all authors of this book for their contributions.

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University Hopital La Pitié-Salpêtrière, Paris, France — Olivier Chosidow

Contents

Part I

History of Scabies

The European History of Scabies Research

1

Michel Janier

Scabies is "*a skin disease produced by an animal parasite, the sarcopt or* Acarus scabiei *and characterized by a specific lesion (the acarian eminence and the burrow*)." This is the definition given by Bazin, the one we can find in the Dechambre dictionary (1880) [1], not so far from the current definition: ectoparasitosis due to a strictly human acarus *Sarcoptes scabiei hominis*.

A simple definition for a simple disease, the obvious parasitic origin of which could have been discovered as soon as the early seventeenth century, when first microscopes were constructed, and even earlier on, the parasite being visible with a naked if somewhat myopic eye, had minds been in capacity of accepting this hypothesis. This was not the case and the parasitic nature of the disease would only be fully accepted at the very end of the nineteenth century. History of scabies is an unbelievable medical saga spanning the whole nineteenth century.

1.1 The Sarcopt

At the center of the stage is an eight-legged animal, the sarcopt, we will alternatively name mite, acarus, acare, siro, parasite, animalcule, creature, stranger, insect (although it is in no way an insect), or bug. The official identity of the sarcopt whose godfathers are Linné (1758) and Latreille (1802) is the following: Kingdom: Animalia; Phylum: Arthropoda; Class: Arachnida; Subclass: Acari; Order: Sarcoptiformes; Family: Sarcoptidae; Genus: *Sarcoptes*; Species: *Sarcoptes scabiei* (from Greek σαρξ: flesh and κοπτω: I cut.).

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1.2 The Dark Years

The French name of *gale* (written as *galle* for many years) is of obscure origin. In ancient Greece, it was called ψωρα (from ψαω: I rub), and in Latin, *scabies* (from scabere: to scratch), the name still used in English. The German calls it *Krätze*, the Spanish *sarna* or *roña*, and *rogne* in Provençal language.

The disease was classified successively in the group of cachexias, vices, phlegmasias, oxygenoses, pustulae, vesicles, and infundibulae.

It was not until 1834 that the sarcopt was identified and its responsibility as the true agent of scabies was accepted only in the second part of the nineteenth century. Yet, the mite had long been known by poor individuals such as Corsican women, Asturian peasants, Orinoco Indians (Humboldt 1800), or galley-slaves from Livorno [2]. Moreover, some ancient authors had made quite good descriptions of the human mite, and the animalcules were perfectly known in animal mange.

We acknowledge that there is no good clinical description of scabies in Hippocrates and Aristoteles, psora being a generic name encompassing many squamous and furfuraceous skin diseases and all itching dermatoses having been named scabies. Many prestigious names in Medicine have tried to elaborate scientific theories to explain the disease. Celse attributed psora to an internal vice of humors, Galien to melancholic ones, Avicenna to a mixture of atrabile, blood, and slime, and Lorry and Hahnemann to dyscrasias.

1.3 The Pioneers

Avenzoar from Sevilla (twelfth century) in his "*Teyssir*" describes the "*souab*" or "*assoab*" which lives in the skin out of which a very little animal can be extracted. But we are not sure of the precise nature of the mite. In 1580, Scaliger named *A. siro* or acarus, a kind of louse living under the skin where it digs galleries. At the same period, Ambroise Paré, the famous French surgeon, describes "*animalcules which dig winding routes under the skin, crawl and gnaw progressively the skin, mainly on the hands while exciting untoward itching*" [2]. Thomas Mouffet (London 1634) in his "Insect Theater" (*Insectorum sive minimorum animalium theatrum*) gives description of *A. siro* which is not a louse and can be found away from the pustules. Both in Germany, Hauptmann (1657) and Ettmüller (1682) using the first microscopes draw imperfect pictures of the mite. A decisive step is made in 1687 in Livorno when Cosimo Giovanni Bonomo, a pseudonym of Diacinto Cestoni, a chemist, publishes a letter sent to the poet and naturalist Francisco Redi. In his "*Osservazioni intorno a pellicelli del corpo umano,*" we can find a good description of scabies and its mite: "*with the tip of a pin, we were lucky enough to catch and observe … from vesicles and pustules … under the microscope, a very small white globulle, scarcely discernible: observing it with a microscope, I found it to be a very minute living creature, in shape resembling a tortoise, of whitish colour, a little dark upon the back, with some thin and long hairs, of nimble motion, with six feet, a sharp head, with two little horns at the end of the snout*" [3] (Fig. 1.1). The

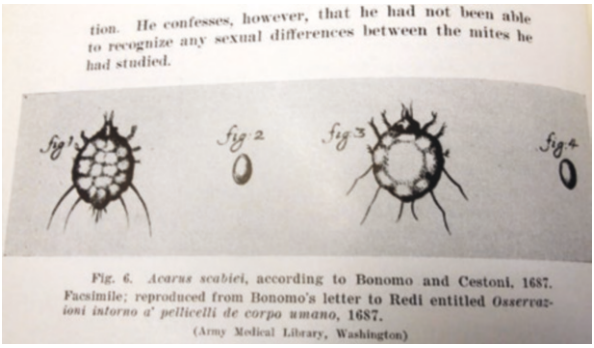

tion. He confesses, however, that he had not been able to recognize any sexual differences between the mites he had studied.

fig. 1 fig. 2 fig. 3 fig. 4

Fig. 6. *Acarus scabiei*, according to Bonomo and Cestoni, 1687. Facsimile; reproduced from Bonomo's letter to Redi entitled *Osservazioni intorno a' pellicelli de corpo umano*, 1687.
(Army Medical Library, Washington)

Fig. 1.1 Bonomo 1687 in ref. [3]

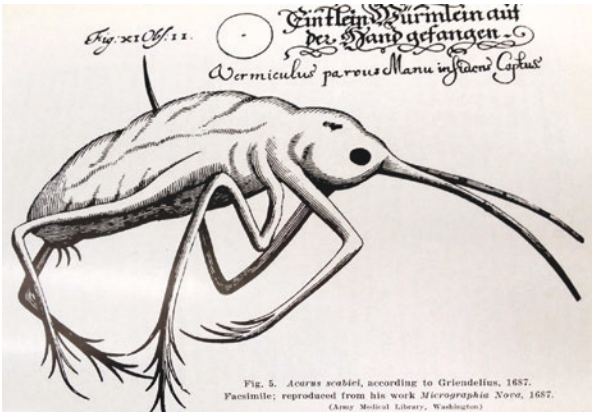


Fig. 5. *Acarus scabiei*, according to Griendelius, 1687. Facsimile; reproduced from his work *Micrographia Nova*, 1687.
(Army Medical Library, Washington)

Fig. 1.2 Griendelius 1687 in ref. [3]

experiment was made on several people, using a primitive microscope and a drop of water. The disease was considered as highly contagious; the mite digs burrows, crawls under the skin, lays eggs, and survives 2–3 days in clothes. Internal treatment is useless and only external treatment must be used, but recurrences are frequent, so several successive treatments may be necessary, because all eggs have to be destroyed. The only inaccurate statements in this pioneer description were the number of legs of the mite (six) and the best place to find it (vesicles and pustules) [4, 5]. Some good drawings of the mite were made by Colonello, differentiating it from the cheese siro [6, 7]. The excellent description made by Bonomo is far ahead of its time, while Heintke (Leipzig 1675), Griendelius (Nuremberg 1687) (Fig. 1.2), and Leeuwenhoek (Delft 1695) continue to draw monsters on their plates, at best confounding the human sarcopt with the cheese mite (*Tyroglyphus domesticus*).

During the eighteenth century, the defenders of Bonomo, such as Linné, successively classified the scabies mite within insects and lice and finally identified it with the cheese mite. This equation was denied by Carl de Geer, a pupil of Linné, who clearly made the difference between the two mites in his "*Mémoire pour servir à l'histoire des insectes*" (1778) [2] (Fig. 1.3). Further progress was made by Johann Ernest Wichmann (Hannover 1786) ("*Aetiologie der Krätze*") and by John Adams (Philadelphia 1807), for refining the description of the bug [4, 5].

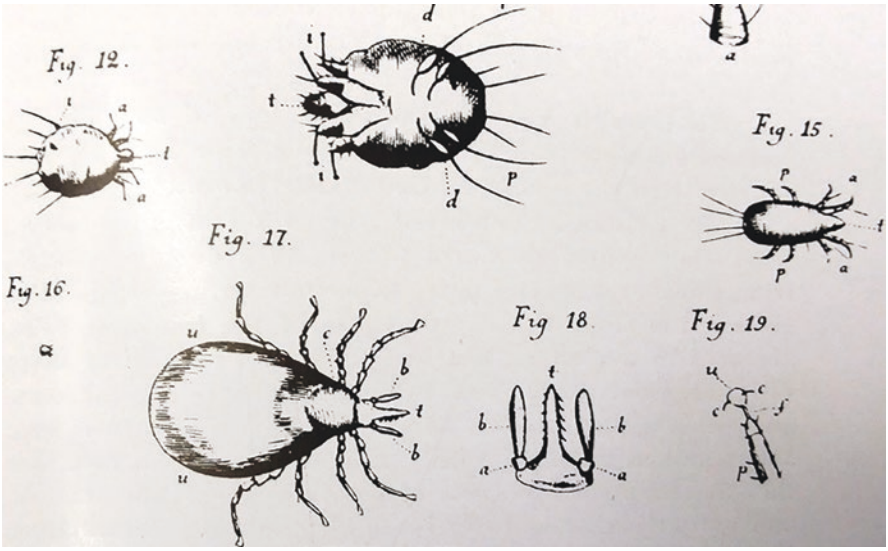


Fig. 1.3 de Geer 1778 in ref. [3]

One could think the case was definitely heard but by no means. These descriptions and theories belonged to single individuals, physicians, and naturalists. But the Faculty had forgotten or neglected them. More than ever, scabies was thought to be due to internal causes such as vice of humors. Allen (1742), in his "*Traité des maladies de la peau,*" wrote "*The unbearable itch which goes along with scabies has led some authors to suspect that this disease was mainly produced by little animals, explaining why it is so contagious, but we did not find any clear statement on that point except what we can find in the philosophical transactions of Bonomo*" [8]. Lorry in his "*Tractatus de Morbis cutaneis*" (1777) underlined that nobody had never seen again the insects of Bonomo and that even if such animalcules could be sometimes found, this could explain neither internal scabies nor the cure of severe diseases by psoral inoculation. The most advanced minds, those who believed in the acarus, thought it was not the cause but the consequence of the disease. John Adams himself believed scabies to be an internal disease. External treatment could even be harmful, repelling the vice into the body. Although contagion was well-known, there was confusion between different skin diseases, itchy or not, such as eczema, lichen, impetigo, and even leprosy. Thus, Allen wrote (1741) "*malignant scabies ordinarly degenerates into leprosy*" and "*I saw several scabetic patients who came back from Bath with confirmed leprosy*" [8]. At the turn of the nineteenth century, in Paris and London, although Biett, Alibert, and Willan firmly believed in the acarus, it was lost again, remaining hidden, although multiple attempts were regularly made to find it.

1.4 The Lamentable Story of Jean-Chrysanthe Galès (1812–1829)

The Imperial Academy of Medicine had promised a grant to whom would discover or rediscover the sarcoptic mite, and Alibert had just arrived in Hôpital Saint-Louis where he founded the First School of Dermatology. Alibert firmly believed in the acarus, as Biett and Willan also did, but the mite remained desperately hidden, and multiple attempts regularly failed to find it again. After one of his famous public lessons under the limes of the Royal Pavilion, Alibert was approached by a student called Jean-Chrysanthe Galès who was in search of a doctoral thesis subject (1812). Galès was born in Betbèze near Toulouse. He had been appointed as chief pharmacist of Hôpital Saint-Louis in June 1802 and also studied medicine in parallel. Alibert was prone to witticism and had a theatrical sense of humor. Playing on words (Galès and gale i.e. scabies), he proposed to the student: "*Write your thesis on scabies, your very name lets you pretend to it*" [9]. Alibert could not imagine this bad joke was to severely shake his reputation and threaten his Empire. A few weeks later (May 26, 1812), Galès announced to Alibert he had discovered the mite, assuring he was successful many times. Alibert organized confrontations and meetings to confirm these findings, before physicians, naturalists, entomologists, members of the Academy of Medicine, and members of the Academy of Sciences and of the General Council of the Paris Hospices. A commission of enquiry of the Academy of Medicine under the presidency of Latreille officially recognized Galès as the discoverer of the etiology of scabies and gave him the price, creating a new genus and species *Sarcoptes scabiei.* Within a few weeks, Galès became famous, extracting the mite "*with as much facility as one used to have trouble finding it before,*" wrote his thesis ("*Essai sur le diagnostic de la gale, sur ses causes et sur les consequences médicales pratiques à déduire des vraies notions sur cette maladie*") (August 21, 1812) [10], and opened a private center for sulfur fumigations in Paris [9]. Galès was always accompanied by a medical student (Patrix) and by Meunier, an engraver of the Natural History Museum, whose duty was to draw the "fabulous insect" on plates (Fig. 1.4).

But nobody was able to confirm these findings, and doubts began to settle concerning the intellectual honesty of Galès. Cuvier himself was surprised by the similarity between the creatures of Galès and cheese mites, far from the drawings of de Geer. Although Alibert's attempts to find the sarcopt, according to the method of Galès, were all vain, the Master remained confident in him and kept reproducing the strange animal in his textbooks and treaties [12] (Figs. 1.5 and 1.6), and even in the Medical Sciences Dictionary (1816) until 1829 [13] (Fig. 1.7). Biett, Lugol, and Rayer were also unsuccessful in Paris, as were Bateman and Willan in England and Galeotti and Chiarugi in Italy. Mouronval, a pupil of Lugol, was complaining in these years: "*I spent my holidays, my free time and recreation hours, surrounded by a multitude of scabetic individuals, using microscope, but I was greatly surprised, the insect refused to appear*" [1] [14].

[1] Eighteen hundred and sixty-seven patients were hospitalized for scabies in Hôpital Saint-Louis during the year 1820.

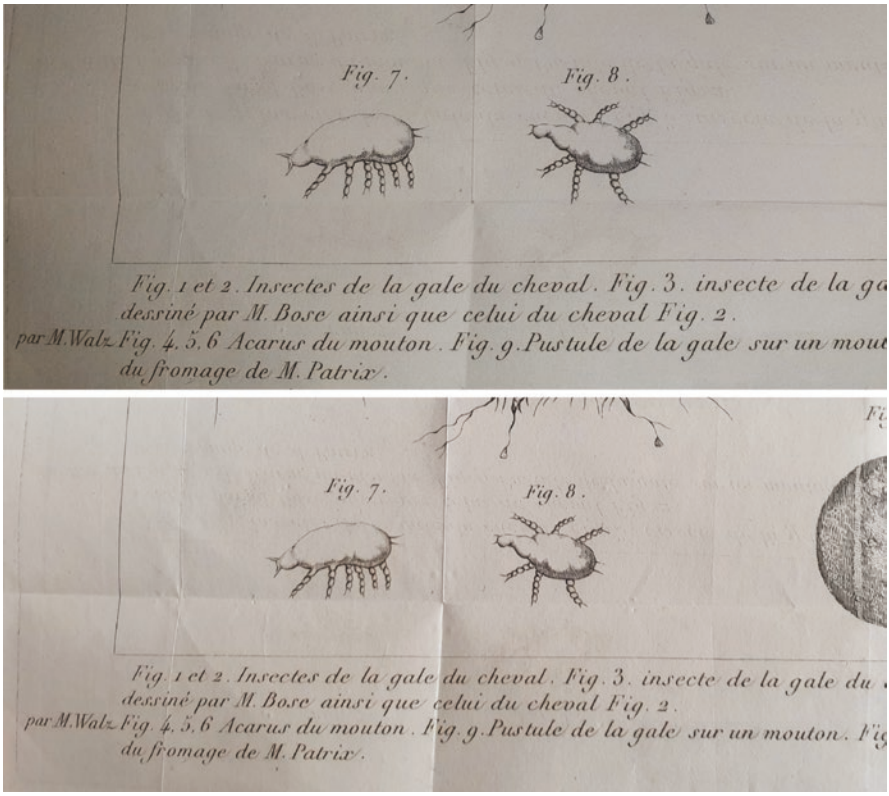
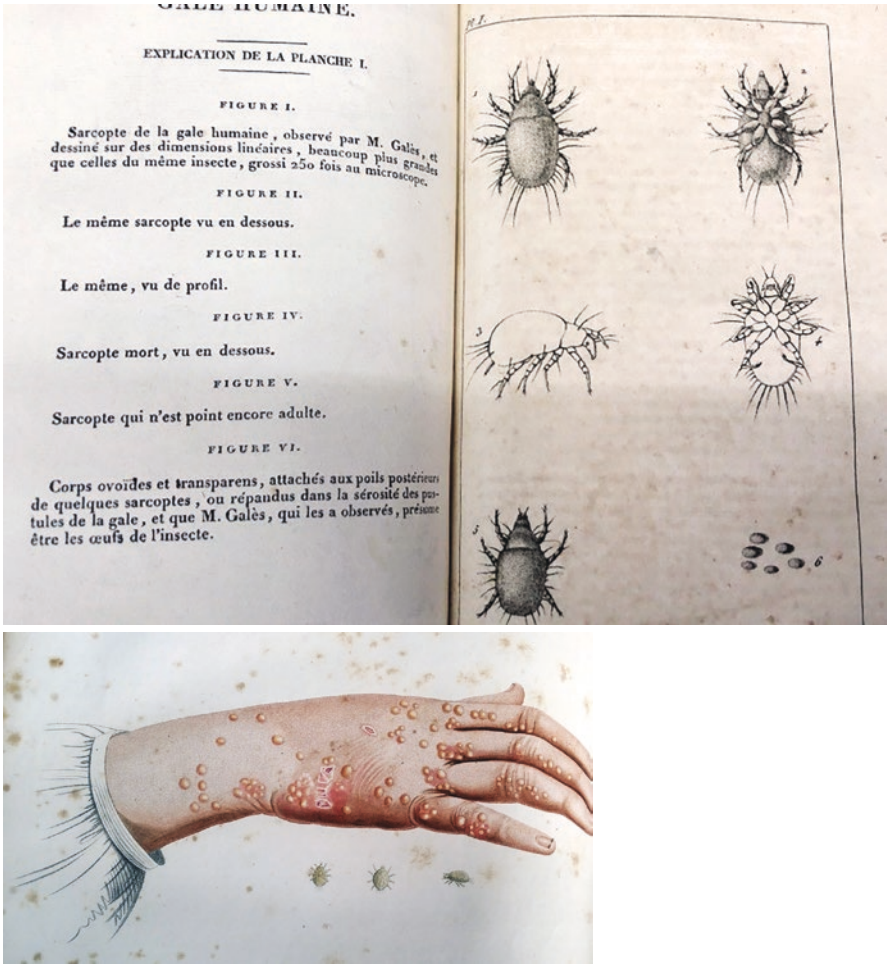


Fig. 1.4 Patrix 1812 in ref. [11]

Galès had left Saint-Louis in 1815 and refused to reproduce his experiments, while Patrix was incapable of finding the acarus again. Mouronval noted [14]: "*Thus the scabies siro, of which one has spoken for 150 years, without having ever seen it and of which imaginary paintings have been made, copied one from the other and never from the original because it is not existing.*" Cazenave wrote in 1828: "*If he is so skilful for spotting the infected vesicles, we need to invite Galès to Saint-Louis. Until he shows us how to do it, we feel authorized to think the acarus is a myth*" [15]. In 1829, Biett and the Willanists took the lead of the anti-acarus party and using the opportunity of this controversy to lead a strong crusade against Alibert himself [16]. The two camps exchanged letters in the *Lancette française* (French Lancet) as sulfuric as the fumigations of Galès, who in the meantime had opened several bath houses in Paris for this purpose. The *coup de grace* would be administered by Raspail, one of the most brilliant scientist of the time. Raspail believed firmly in the existence of the sarcopt, but he was also convinced that Galès was a crook and a hoaxer and that he had substituted the cheese mite to the scabies acarus. Raspail found a strong ally in Lugol, a new head of a dermatology department at Saint-Louis and competitor of Alibert. Lugol promised a 300 francs (100 British crowns) price to the student who would discover the acarus. Patrix and Arnal, a student under Lugol, exchanged



GALE HUMAINE.

EXPLICATION DE LA PLANCHE I.

FIGURE I.

Sarcopte de la gale humaine, observé par M. Galès, et dessiné sur des dimensions linéaires, beaucoup plus grandes que celles du même insecte, grossi 250 fois au microscope.

FIGURE II.

Le même sarcopte vu en dessous.

FIGURE III.

Le même, vu de profil.

FIGURE IV.

Sarcopte mort, vu en dessous.

FIGURE V.

Sarcopte qui n'est point encore adulte.

FIGURE VI.

Corps ovoïdes et transparens, attachés aux poils postérieurs de quelques sarcoptes, ou répandus dans la sérosité des pustules de la gale, et que M. Galès, qui les a observés, présume être les œufs de l'insecte.

Figs. 1.5 and 1.6 Alibert 1814 in ref. [12]

violently in the *Lancette Française*: Arnal: "*who will believe that battalions of bugs are maneuvering under the skin.*" Patrix: "*I saw them with a naked eye on the mirror of the microscope.*" Arnal: "*they were probably sledging*" [17, 18]. On September 2nd, 1829, a Royal Navy surgeon named Meynier announced he would compete, and a public demonstration was organized in Saint-Louis before Lugol and several important scientists. Meynier took a sample from the vesicles of a scabetic patient, stirred it in a drop of water with his own fingernail under the microscope, and let the acarus appear in front of an enthusiastic audience who recognized the insect of Galès. But the triumph of Alibert would be of short duration, as a few days later, Raspail revealed Meynier was his emissary and that he had organized a mystification, Meynier putting under the microscope with his nail some mites proceeding from damaged cheese he had brought with him, hidden in his pocket [19]. It was a real

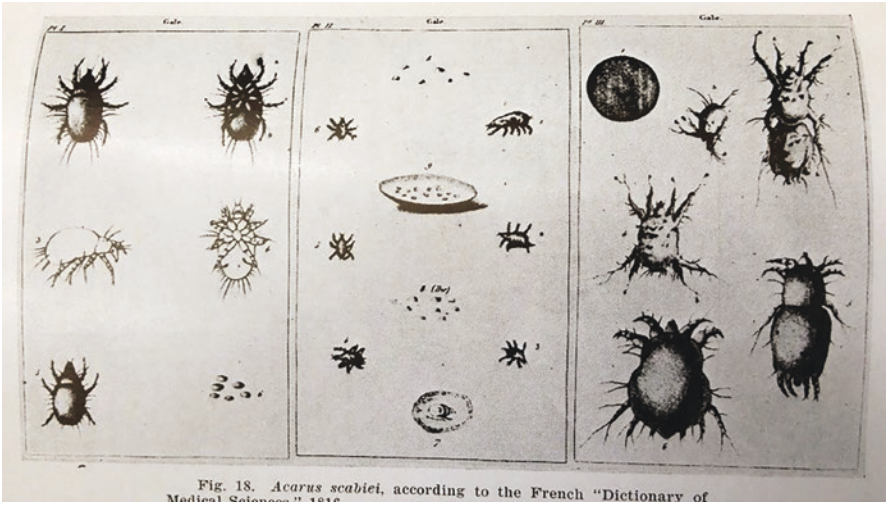


Fig. 1.7 Gale in Dic Sciences Médicales 1816 in ref. [13]

disaster for Alibert's reputation, and Latreille suppressed *Sarcoptes scabiei* from the nomenclature (October 22nd, 1829). A final confrontation would be organized in the Hôtel Dieu de Paris in Dupuytren's department on October 25th, 1829, and Alibert was being morally forced to accept the challenge. Patrix was sent to the front, but Alibert, Lugol, Latreille, and Dupuytren wisely avoided the party where several scabetic patients were invited among an accumulation of water baths. It was an absolute fiasco. Patrix could not find the acarus. In a theatrical attitude, Raspail stood up, took some damaged cheese from his pocket, and dusted it on Patrix slides, declaring the damaged cheese had cost him more than fresh one. A blame was given to Patrix by the Faculty, but everybody knew it was addressed indirectly to Alibert.

The French Revolution of 1830 occurred while the whole medical community was disenchanted and had abandoned all hopes of ever discovering the sarcopt.

Galès was judged severely by most of his contemporaries. Devergie: "*this inventor deserves reprobation and contempt*" [2]; Biett: "*this constant success on one side and this permanent failure on the other left in mind a somewhat irrepressible doubt*" [15]; Raspail "*Galès has falsely shown the cheese mite for acquiring easy glory and money*" [19]; Cazenave " *One can question the sincerity of this chemist*" [16]. Galès was probably a crook. At best, after discovering by chance the sarcopt in a vesicle, he perpetrated a fraud for self-esteem, lucre, and notoriety reasons. Galès made a fortune with his sulfur bath houses and died in 1854 without ever answering the criticisms of his peers.

1.5 The Wonderful Story of Simon-François Renucci (1834)

Simon-François Renucci was born in Cozzano (Corsica) (1794) and had frequently seen Corsican women extracting the acarus from the skin. He also performed it himself many times but, as already underlined by Thomas Mouffet and Wichmann,

the acarus was not to be searched in the vesicle but at the end of the burrow, where one can see the clue, i.e., "*a white dot whose distance from the vesicle has kept apart for centuries failures from success*" [11, 20]. As a medical student at the Hôtel-Dieu de Paris, he was astounded by the lamentable state of the current medical knowledge about scabies. He was attending regularly Alibert's lectures in Saint-Louis and convinced the Master he would be successful in finding the acarus. "*Thus, as soon as July 13th 1834, noticing, attending the consultation of this doctor, a young lady … with numerous scabetic vesicles on her hands and who had not received any treatment, I announced positively to all doctors and students here that they would see the fabulous insect soon. And indeed, I performed the extraction with a needle. The siro walked easily upon my nail, and everyone could see it with a naked eye. I was prayed by the crowd of spectators to repeat the operation on another scabetic patient, and the same result had to occur rapidly. Professor Alibert ordered to draw up the minutes, which were signed by all of us and sent to the Faculty. This discovery was inserted in the* Gazette des Hôpitaux *and found as many doubters as believers*." [11]. The experiment was reproduced in public on August 20th, 1834, and Lugol (a Willanist disciple of Biett), making fun of Alibert, renewed his price "*Alibert has suspended his holidays while he needed them so much. He is very brave, at the end of his career, after such tremendous defeats to come back into battle … I renew my 300 francs price for the student who will find the sarcopt*" [21, 22].

On August 25th, 1834, the session was announced in the *Gazette des Hôpitaux* and took place in a neuter department of Saint-Louis (the clinic of Emery), at 9 o'clock a.m.; the weather was good, a sunny day, and the audience was large: Raspail, Pinel, Lugol, Sabatier, Legros, Alibert, and Emery were present. At 10 o'clock a.m., Renucci extirpated the acarus with a needle, and put it under the microscope. Emery reproduced the experiment, and Raspail recognized the similarity between this mite and those of the plates of de Geer [23]. Lugol had to admit his defeat. From that very day, the existence of the acarus would never be questioned again.

Renucci published his discovery in his thesis ("*Thèse inaugurale sur la découverte de l'insecte qui produit la contagion de la gale, du prurigo et du phlyzacia*") (April 6th, 1835) (Fig. 1.8) [11] in which he underlined the impossibility of finding the insect in the vesicle fluid. After a triumphant tour of different hospitals in Paris (the clinics of Rayer, Ricord, and Cloquet), Renucci would disappear discreetly, going back to Corsica. He was appointed *chevalier de la Légion d'Honneur* for devotion and courage during a cholera epidemic in Constantine and died in 1884 as a beloved doctor in Corsica [24].

The benefits of this discovery went to Raspail and to Alibert who quickly brought modifications to his plates (Fig. 1.9) [25]. But until the end of the nineteenth century, many scientists still believed the acarus was not the cause but the consequence, the product of the disease (the spontaneous generation theory), scabies being due to dirtiness, misery, and debauchery. Thus, Devergie said: "*The identification of the acarus with the disease is a pure induction of mind. The burrow generates the acarus*" [26].

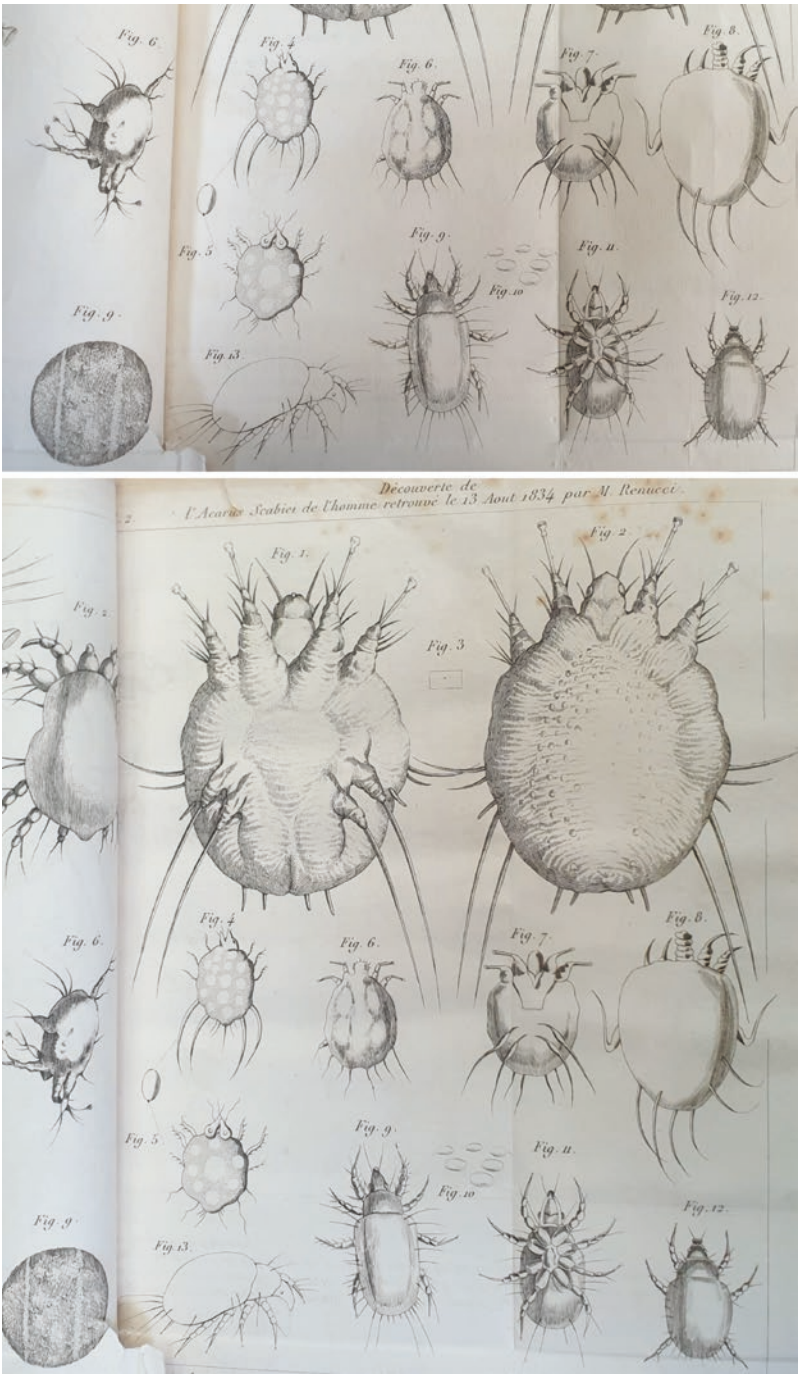


Fig. 1.8 Renucci Thèse 1835 in ref. [11]

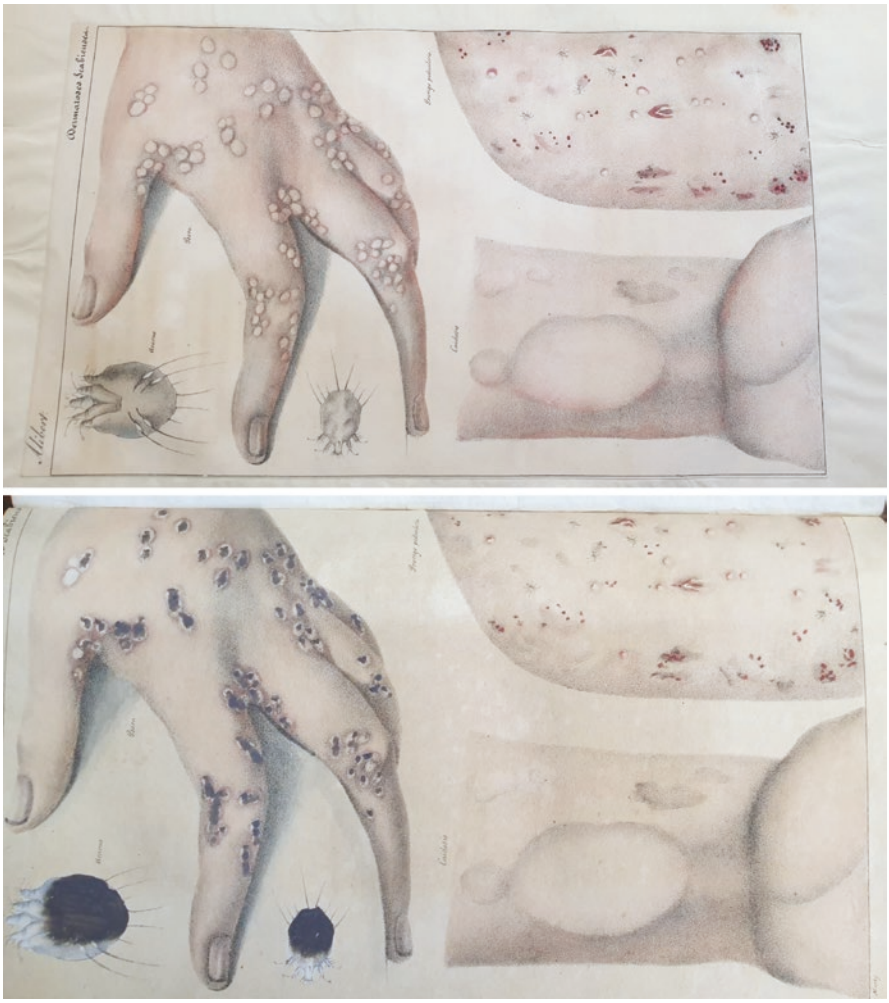


Fig. 1.9 Alibert 1835 in ref. [25]

1.6 Treatments

Until the end of the nineteenth century, internal treatment (astringents, sorbents, sudorifics, laxatives, cathartics, purgatives, wood decoctions, snake flesh, elderberry rob, lettuce, scabiosa, whey, sweet clover, chamomile, guaiac gum, hellebore, medicinal beer) was systemically associated with topical treatment. External treatments included lead, mercury, tobacco, camphor, ammonia, ginger, saffron, cade oil, olive oil, turpentine, hellebore, thyme, hypericum, myrrh, hemlock, black soap, couch grass, leadwort, clematis, nitrates, and iodides, but the most popular was sulfurs, already used by Celse. With time, treatments would progressively become simpler. Alibert used the sulfo-alkaline ointment of Helmerich (1812) associating

Fig. 1.10 La frotte in Nekam, ref. [23], p. 157

potash subcarbonate, sublimated sulfur, and hog's lard [11, 27] after vigorous rubbing of the skin with black soap, for 2 weeks, and so did Cazenave, the head of the Saint-Louis clinic for scabetic patients (1838), although Cazenave, like Hebra in Vienna, favored a localized daub only on the affected areas [28, 29]. Duration of hospitalization decreased to 6 days when Bazin took at Saint-Louis' Scabies Pavilion in 1850; and Hardy in 1852 closed the Scabies Clinic when deciding to treat scabies in an outpatient ward with only one 90 min daub called *la frotte* (the rub) (Fig. 1.10) [30, 31]. These treatments were highly irritant and bad-smelling, Cazenave wrote "*It is difficult to consider as a cure the state of these poor devils sent back to their* "garnis" *or workshops … maybe with their dead acarus but certainly with all their pimples, plus on the entire body a coat of ointment which will alter their linen forever and nine times out of ten with a new eruption caused by the treatment.*" Adding "*only strong young males such as soldiers can bear the treatment but in no case women nor society people*" [28]. Washing linen and cleaning the bed were associated, and mites would die after 3–4 days or after heating 20–30 min at 75 °C [11].

Substantial progress was realized later with use of Peruvian balsam (1860), pyrethrins (1930), and benzyl benzoate (1937).

Let's come back to the gentle stranger. Search for the acarus had its days of glory in the year 1850, everybody advocating the easiness of the extraction. Thus, Bazin wrote: "*One has to tear the epidermis with a needle at about one millimeter of the white spot, towards which one proceeds cautiously. Then press the needle under the animalculus which clutches the device, staying still for a while. It looks like a starch grain. But soon it executes movements we can distinguish with the naked eye*" [30]. Devergie (at last convinced!) in 1857 "*The acarus removed from its burrough in winter is numb with cold, crouched, curled up, motionless. If you put it closer to the fire, you can see it making rapid movements. Put in oil of cade, it fusses, seems worried, surprised, then stiffens and stands still*" [26]. Lanquetin wrote: "*One gently introduces a needle in parallel to the skin. If the operation is correctly done, one must see the sarcopt clutching the needle. This little operation is extremely easy. You need only a little practice and a normal view*" [2]. But there are also some scoffing spirits. Thus, Augé in his book named "*Comment diagnostiquer la gale quand on*

n'est pas dermatologiste" [32] wrote "*In these days when each physician sees twenty times more patients than he can seriously examine, do you really believe he will be able to spend 2 h to characterize a sarcopt perched on top of a needle.*"

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Part II

Parasitology and Basic Research

2 Biology of *Sarcoptes scabiei* and Its Relevance to Human Scabies: Clinical Symptoms, Treatment, and Management

Rie R. Yotsu, Junko Yoshizumi, and Arezki Izri

2.1 Introduction

Human scabies, an itchy and contagious skin disease, is caused by infestation of the skin by the mite *Sarcoptes scabiei* variety (var.) *hominis*. Scabies occurs in all socio-economic levels independent of hygienic conditions [1]. Based on the report of Global Burden of Disease (GBD) in 2015, scabies was responsible for 0.21% of DALYs (Disability-Adjusted Life-Years) worldwide [2]. In 2016, GBD estimated that scabies is responsible of DALYs in about 3.8 million people [3]. In the developed world, the severe forms of disease are commonly reported in the elders, immunocompromised individuals or those with deteriorated general condition [4]; while in the developing world, scabies can affect any population [5]. Scabies is endemic in many tropical developing countries, with an estimated average prevalence of 1% to 2% in children but could be over 20% in highly endemic communities [6]. Since

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2017, it is listed as one of the neglected tropical diseases (NTDs) by the World Health Organization and global efforts are being made for better control of the disease [7].

There are several known risk factors for acquiring human scabies—however, how transmission occurs is yet uncertain. Although some differences among racial groups have been described, they are probably more attributable to socioeconomic and behavioral factors. Overcrowding is an important factor in the spread of scabies. Closed communities and institutional environments experience high endemic rates and epidemic outbreaks both in tropical and developing countries [8–12]. The role of hygiene is controversial; some studies imply that better hygiene reduces the prevalence of scabies with also reduced prevalence of impetigo [12, 13] whereas other studies state that the hygiene is not a significant factor for scabies infestation [14, 15]. The latter is supported by the fact that scabies is also seen in the most developed countries with high standards of hygiene.

When we take a look at the clinical manifestations of scabies, scabies is a great "masquerader" which can mimic other skin diseases like eczema, prurigo, asteatosis, and even rarer ones such as psoriasis, bullous pemphigoid, or erythroderma. Identifying the mite from the skin is the only way to confirm the diagnosis of scabies, but this could be challenging even sometimes for specialists. There is also no established point-of-care diagnostic test available for scabies yet, which poses further challenge for the less skilled personnel.

For any disease, it is important to understand how the disease is transmitted to establish preventative measures, and this comes with understanding of the biology of the pathogen—including its morphology, life-cycle, and physiology. Better understanding of the pathogen also contributes in improvement of its diagnosis and treatment. The same goes with scabies, and it is necessary that we know more about the mite in order to improve on our preventative measures, diagnosis, and treatment. In this chapter, we will provide the updated knowledge of the *Sarcoptes scabiei* var. *hominis* mite—what we know of this mite to date—with an aim to bring some insights into how we could better control for this ectoparasitic disease seen worldwide.

2.2 History of Scabies

The name *Sarcoptes* comes from the Greek words *sarx* meaning "flesh" and *koptein* meaning "cut," and *scabiei* from the Latin word "scabere" meaning "to scratch" [16]. The disease has been known for over 2500 years and the Greeks and Romans were the first to document about this disease [17, 18]. The archeological evidence certifies the presence of this disease in Egypt and the Middle East as early as 494 BC. In the fourth century BC, Aristotle reported it as "lice" that "escape from little pimples if they are pricked." Later, Roman medical writer Aulus Cornelius Celsus described it by giving the name "scabies" [18, 19]. Nevertheless, not much was known about the disease until 1687 when Giovanni Cosimo Bonomo and Diacinto Cestoni from Italy identified the causative organism using light microscopy [18, 20]. Their report was one of the first official descriptions explaining well the etiological cause. Afterward however, several primitive reports followed which documented on this disease without making successful connection of causality. In 1746,

Carl Linnaeus, the Swedish naturalist, classified the mite as *Acarus humanus subcutaneous* [21]. The first illustrative description with nomenclature name of the mite, *Acarus scabiei*, was given by the Swedish entomologist Charles De Geer in 1778 [22]. The mite's nomenclature has evolved since then, now called the *Sarcoptes scabiei*, together with more understanding of the mite.

2.3 Bio-Entomological Features of *Sarcoptes scabiei*

2.3.1 Classification

Sarcoptes scabiei belongs to the class of Arachnida and the family of Sarcoptidae along with other ectoparasitic mites of mammals (Table 2.1). Like other arachnids, scabies mite is an eight-legged arthropod. It is further differentiated from other arachnids by the position of a distinct "gnatosoma" (mouth part) and the lack of a division between the cephalothorax and the abdomen [23]. Today, *Sarcoptes scabiei* is commonly agreed that it is one species, while some subspecies exist adapted to live in different hosts. Besides *Sarcoptes scabiei* var. *hominis* that is an obligate subspecies parasites on humans, there is *Sarcoptes scabiei* var. *canis* found in dogs and *Sarcoptes scabiei* var. *vulpis* found in fox, as other common ones [24].

2.3.2 Morphology

The adult mite has an oval tortoise-like shaped body ("idiosoma") bearing four pairs of legs: two pairs in front and two pairs behind. Figure 2.1 is showing the image of the mite using stereomicroscopy, and Fig. 2.2 is showing the mite's features under microscopy with potassium hydroxide (KOH) preparation (×100 magnification). It does not have an evident head, but has a mouth part that looks like a turtle head. This anterior region is called the "gnathosoma" and contains specialized feeding appendages ("chelicerae") and segmented structures called "palps" or "pedipalps" [25]. The scabies mite does not have eyes. The surface of the body is covered with fine

Table 2.1 Classification of *Sarcoptes scabiei*

Taxonomic rank	Nomenclature	Established
Kingdom	Animalia	Linnaeus, 1758
Phylum	Arthropoda	Latreille, 1829
Subphylum	Chelicerata	Heymons, 1901
Class	Arachnida	Cuvier, 1812
Subclass	Acari	Leach, 1817
Superorder	Acariformes	Leach, 1817
Order	Sarcoptiformes	Reuter, 1909
Suborder	Astigmata	–
Family	Sarcoptidae	Murray, 1877
Subfamily	Sarcoptidae	–
Genus	*Sarcoptes*	Latreille, 1802
Species	*Sarcoptes scabiei*	Latreille, 1802

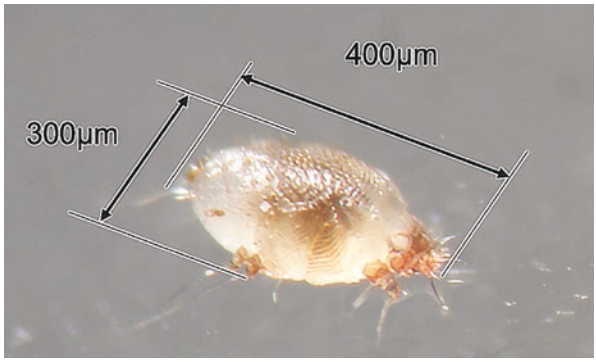

Fig. 2.1 Lateral view of a fertilized female *Sarcoptes scabiei* var. *hominis*. (Photo of stereomicroscopy: Yasuo Wada)

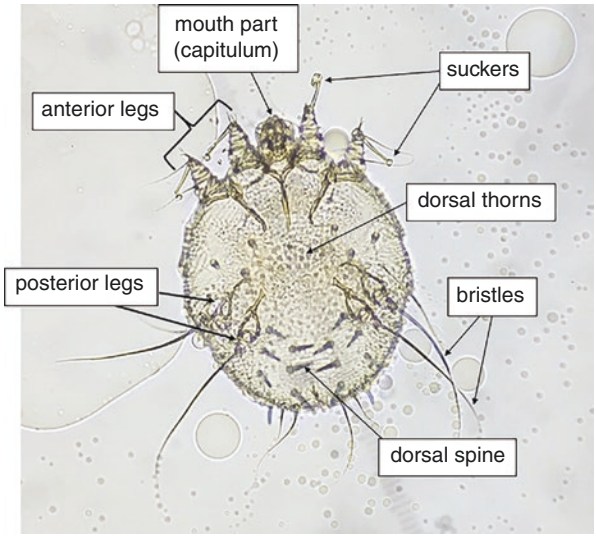

Fig. 2.2 A fertilized female mite under microscopy at ×100 magnification

Table 2.2 Average body size of *Sarcoptes scabiei* var. *hominis* in different life stages [27]

Stage	Size (μm)		No. of pairs of legs
	Length	Width	
Egg	170	90	NA
Larva	150	100	3
First nymph	170	140	4
Second nymph	240	200	4
Male mite	220	170	4
Young female mite	325	250	4
Fertilized female mite	400	300	4
Scybalum	30	15	NA

NA not applicable

striations and dorsally bears a number of stout thorns and spines. The frontal two pairs of legs end in suckers and the posterior two pairs end in long bristles. The anal opening is terminally located [26].

The size of an adult female mite is approximately 400 μm in length and 300 μm in width, and with its cream colored body, it is hardly visible by the naked eyes (Table 2.2). However, it can be visible when the scabies burrow (described in the following sections) is examined by a hand-held dry dermoscope with ×10 magnification. This allows visualization of the mouth and the base of the anterior legs of the fertilized female mite, which are brown in color, through the stratum corneum of human skin [28].

The sarcoptes, unlike the hexapod (six-legged) insects, have no wings or antennae. Although the mites cannot fly or jump, they may crawl as fast as 2.5 cm/min on warm skin [29, 30].

2.3.3 Life Cycle

The life cycle of *Sarcoptes scabiei* var. *hominis* includes four stages: (1) egg, (2) larva, (3) nymph and (4) adult. The entire developmental life cycle takes almost 2 weeks (Fig. 2.3).

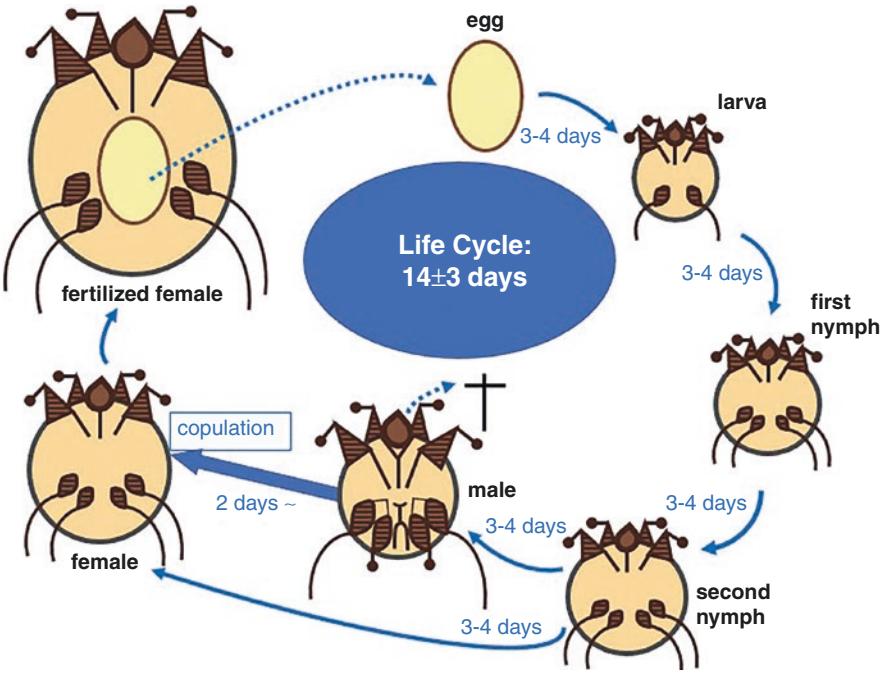

Fig. 2.3 Life cycle of *Sarcoptes scabiei* var. *hominis*

Fig. 2.4 Microscopy of scraping of the burrow at ×100 magnification

2.3.3.1 Egg

The fertilized females lay 2 to 3 eggs/day in the burrows. Eggs are whitish oval shape with the width of 0.09 to 0.10 mm and length of 0.17 to 0.19 mm (Table 2.2). The egg hatches within 3 or 4 days, giving rise to larva [31]. The shells are often broken vertically and the empty shells are left after hatching (Fig. 2.4).

2.3.3.2 Larva

After hatching the eggs, the larvae migrate to the intact stratum corneum to construct a short burrow called a molting pouch. The larva looks almost like its parents but is smaller in size and has only three pairs of legs. The larva casts its larval exuvium in the molting pouch after 3 to 4 days, giving rise to the first nymph [23].

2.3.3.3 Nymph

The nymph looks similar to its parents with four pairs of legs. The nymphs, like larvae, may often be found in the molting pouches or in the hair follicles. The first nymph (protonymph) molts after 2 to 5 days and gives rise to the second nymph (tritonymph). The second nymph looks like an adult female mite but has no genital organs. The second nymph molts after 5 to 6 days and becomes an adult [32].

2.3.3.4 Adult

The young females are about 0.32 mm in length and 0.25 mm in width. Mating takes place only once when the male mite finds the young female in her molting pouch, which leaves the female fertile for the rest of her life. The development of the ovaries after mating enlarges the female's body, making fertilized females twice as bigger than the males (about 0.22 mm in length and 0.17 mm in width) [32, 33]. The fertilized female mite, about 0.4 mm in length and 0.3 mm in width, is the biggest form and found at the end of the burrow. After mating, the male mite dies. The female mite emerges from her molting pouch, walks on the skin, and when she finds a suitable location for laying her eggs, start to burrow beneath the skin again [23, 25]. It takes about 30 min to an hour for the female mite to submerge herself in the stratum corneum [27, 33]. The mites never go below the stratum corneum [33]. While she lays the eggs, up to 3 eggs/day, she makes the characteristic serpentine burrow at the speed of 0.5 to 5 mm/day [33]. She lays a total of 40 to 50 eggs during a life span of well over 30 days, or 26 to 40 days [25, 33]. Under optimal conditions, it is known that about 10% of the eggs make it to the next adult stage [34, 35].

2.3.3.5 Scybalum/Scybala

Scybala are fecal pellets produced by a fertilized female mite. They are sometimes found with eggs and/or fertilized female mite in the scraping of the scabies burrow. They are small oval shape, yellowish-brown in color, and about 30 μm in length and 15 μm in width.

2.3.4 Physiology

Understanding of the physiology of *Sarcoptes scabiei* var. *hominis* has advanced in recent years, and several important—and interesting, factors have been identified in which shows how the mites survive in the host skin. The mites produce molecules such as digestive proteases and complement inhibitors, and perhaps some more molecules that help them in their survival. The digestive proteases are known to mediate a range of essential physiological functions of the mite, including tissue invasion and migration, digestion, molting, and reproduction. The mites also produce inhibitory molecules in their gut that block complement components of the host, enabling them to escape from the complement-mediated damage that they may cause [36].

In a study by Mohmood et al., they tested the mite protease activity and found that it was capable of digesting human hemoglobin, serum albumin, fibrinogen, and fibronectin, but not collagen III or laminin [37]. This is interesting as collagen III and laminin are structures of the basement membrane of the skin, and this may explain why scabies mites are restricted in the epidermal layer of the human skin [37]. They reside mainly at the interface of the stratum lucidum and stratum granulosum where intercellular fluid is close to the mite's location and seep into the burrow [38, 39]. By deep burrowing in the stratum corneum near the living tissue (cells) of the lower epidermis, they ingest intercellular fluid (lymph). Scabies mites secrete saliva that forms a pool around their body. Nevertheless, the procurement of host intercellular fluid appears to be necessary for mites to obtain sufficient water to maintain their water balance [40]. After digestion of necrotic stratum corneum of the skin, the scabies mites leave their feces in the burrow.

Some studies have investigated on relationship between host specificity and potential physiological differences of scabies mites and found that different host-associated scabies mites produce proteins which are immunologically recognized by other host species—which could trigger immune response, as well as some proteins which are only recognized by their host [41]. Several recent studies of mite genetics additionally support the host specificity of scabies mites [42]. As our technology advances, genomic and transcriptomic studies will allow further understanding of the scabies mites and its pathogenesis in humans and in other animals.

2.3.5 Vectorial Role

Sarcoptes scabiei var. *hominis* does not suck human blood for their survival. Despite the scabies mites being coexistent with humans since the biblical times, there has

been no report in the literature on the mites serving as a vector for transmission of other diseases up to present.

2.4 Transmission of Scabies

The transmission of scabies usually occurs by prolonged direct skin-to-skin contact with an infested individual but sometimes via the shared clothing, towels or bedding. It takes about 15 to 20 min or more of close contact for a successful transmission to happen [16]. *Sarcoptes scabiei* var. *hominis* is known to perceive odor from a live host or body temperature as their stimuli to seek for the source at a certain close distance [25, 43]. Interfamilial transmission is frequently reported, and genotyping results of *Sarcoptes scabiei* var. *hominis* confirm long-held beliefs that transmission events for scabies tend to be localized in time or space, and that the family/household is the main core of transmission [16].

In case of the severe form of the disease, crusted scabies, an extremely high mite burden, and severe crusting of the skin can develop. This form of scabies is highly contagious, and the mites which are shed from the old skin, or the scales, can contain hundreds to thousands of mites, infecting others beyond the very close contacts. Nails are also often affected in crusted scabies. When infected from crusted scabies, the incubation period is known to be much shorter than when infected from common scabies, which is probably due to high number of mites infesting at the same time [31].

Sarcoptes scabiei is also responsible for epizootic disease in livestock and wild animals called "mange." However, it is caused by different subtypes of *Sarcoptes scabiei* mites, which cannot complete their life cycle in humans. Although difficult to make estimates, prevalence of mange is reported to be high, for example, some previous studies have reported on prevalence of mange in pig herds (*Sarcoptes scabiei* var. *suis*) to be between 11% and 95% depending on different regions [44–47].

2.5 Clinical Symptoms of Human Scabies in Relation to the Biology of *Sarcoptes scabiei*

2.5.1 Pathogenesis and Pathology

Clinical features of scabies are caused by the invasion of the mites into the skin. As the burrow is initially not itchy, it often goes unnoticed [27, 48]. However, after about 14 to 30 days of incubation period, itchy red papules start developing on the trunk and extremities. Some vesicles and bullae may also be seen. Intense itching sensation often occurs in body parts where there are no skin lesions. This all happens as a result of a delayed hypersensitivity reaction to the mites, eggs, and scybala (feces). With reinfestation, i.e., history of prior scabies, the sensitized individual may develop a rapid reaction causing earlier symptoms. Understanding the immune

response mechanisms to scabies mites is essential in understanding the pathogenesis of scabies and consequently in improvement of treatment options.

Susceptibility to crusted scabies has been linked with immunosuppression including decreased immunity due to aging [49]. Crusted scabies following systemic and topical steroids has been reported, which is the most common idiopathic cause of the condition [50–52].

2.5.2 Clinical Presentations

Initial clinical signs include small papules accompanied with short linear burrows which develops into a more serpentine feature as time progresses, highlighting the presence of the mite within the epidermis. Nevertheless, there are sometimes the papules without obvious burrows, or sometimes present with larger lesions (nodules) or with inflammation. Below provides detailed descriptions of each characteristic feature.

2.5.2.1 Burrows

Scabies burrow is a characteristic lesion to scabies. It is a whitish threadlike scaly lesion (Figs. 2.5a and 2.6). The length of the burrows is often up to 5 mm but can be longer [1]. The width is almost constant, about 0.4 mm, just over the width of the fertilized female mite. It is slightly raised from the skin level; therefore, it is often palpable.

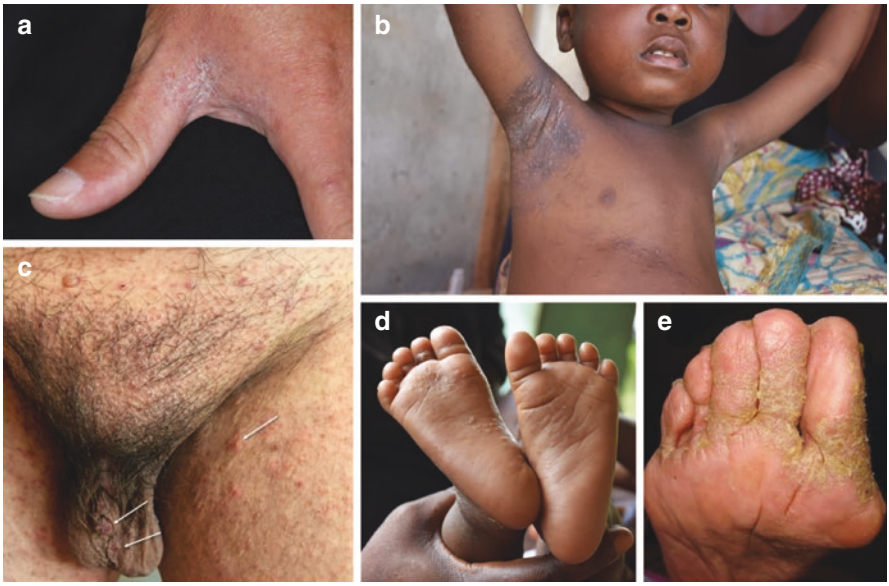

Fig. 2.5 (**a**) Burrows and papules in between the fingers, (**b**) Crusted scabies on the axillae and generalized papules on the trunk, (**c**) Scabies nodules on the penis, scrotum and groin, (**d**) Pustules on the soles of an infant, (**e**) Crusted scabies of the foot in a bedridden patient

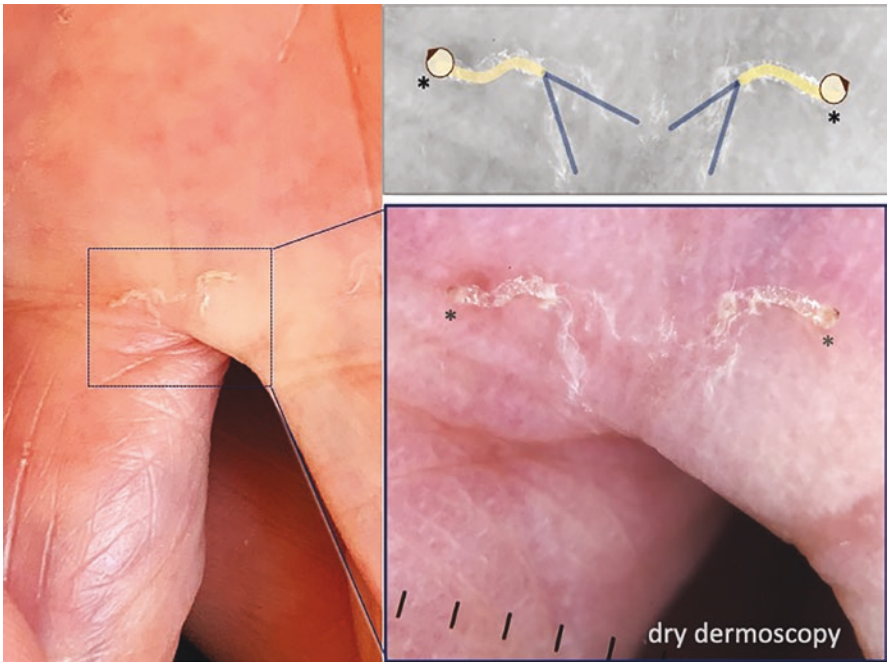

Fig. 2.6 Scabies burrows with the wake sign and fertilized female mites (*) under hand-held dry dermoscope with ×10 magnification (1 scale = 1 mm)

Distributions of the burrows are limited to specific parts of the body. Palms, between the fingers and the lateral sides of the hands are the most likely places to find the burrows [33]. The wrists, elbows, axillae, lower legs particularly the ankles, genital areas in men, and the breasts in women are other places to find the burrows [53]. Burrows can also be found on the surface of freshly developed nodules and/or round erythema. Burrows are not found on the face and head, except for occasionally in infants and bedridden patients.

2.5.2.2 Papules

The emergence of immature mites leads to appearance of itchy red papules within 2 to 5 days where they burrowed. They then move away from their molting pouches within a few days [27]. This is the reason why microscopy of the scrapings of the papules seldom shows the mites, as they have moved to other places by the time the papules develop. Histopathology of the papule shows an inflammatory cell infiltrates, typical of a delayed sensitivity cell-mediated immune reaction [1]. The itchy red papules are not specific to scabies, but the distribution of the papules may help us to suspect scabies [28]. They are usually scattered and do not coalescence. Within few weeks, number of the papules increases gradually. Besides the hands, they are often found on the abdomen especially around the periumbilical region, arms, thighs, axillae, and buttocks (Fig. 2.5a, b) [54].

2.5.2.3 Nodules

The reddish-brown nodules are sometimes found on the scrotum, penis, groin, axillae and buttocks in the later stage of the infestation (Fig. 2.5c). They are bigger than papules, with often 7 to 10 mm in diameter. Occasionally, a scabies burrow can be found on the surface of a freshly developed nodule. They are extremely itchy and the burrow on the surface is often excoriated.

2.5.2.4 Inflammation on the Burrows

Scabies burrows often present with little inflammation at the early stage of the infestation [27, 48]. If the subject had a history of prior scabies, an inflammation can be observed around the burrow and the pruritus can immediately occur when the female mite starts burrowing [29, 33]. The longer the infestation period, the stronger the inflammation can occur around the burrows. Erythema, vesicles, pustules, and in some cases, bullae can be formed around the burrows (Fig. 2.5d).

2.5.2.5 Crusted Scabies

Crusted scabies is rare but is a severe form of the infestation characterized by diffuse or localized hyperkeratotic lesions with a variable degree of erythematous scaly eruption (Fig. 2.5b, e). Hyperkeratotic lesions could be particularly severe on the hands and the feet including palms and soles. Scabies burrows are sometimes seen in the vicinity to the hyperkeratotic areas, but not always.

2.5.2.6 Other Clinical Characteristics

Itching (with or without a rash), which can worsen at night, is the most common symptom. Usually, the face and head are not affected, although they may be involved in cases of infants and young children. Due to the development of immune reaction of the human host against the mite antigens, the itchy small nodules may persist after treatment (known as postscabietic nodules), without presence of the mites. Infants and young children develop inflammation around the burrows earlier and stronger than adults (Fig. 2.5d) [55]. Secondary infections may also occur from the pustular lesions or crusted scales, or from the erosions created from the scratches.

2.5.3 Diagnosis

Clinical diagnosis remains the main method to diagnose scabies. Observation of the burrows in the skin, clinical feature of the lesions, itching sensation that worsens at night and the presence of itching in other members of the family are among the clinical signs that supports its diagnosis [5, 28].

A definitive diagnosis can be made by demonstrating the presence of adult or immature scabies mites, ova or even feces. Searches for these signs involve either scraping a suspected burrow, mounting the sample in KOH and examining it under a microscope, or examining the skin lesion directly by dermoscopy.

The classical sign of scabies is the burrow made by a mite within the skin, and identifying this feature is the key to reaching diagnosis. When examined by a

hand-held dermoscope with magnification of ×10, the burrow could be observed as an irregular serpentine line (Fig. 2.6). If the burrow is lengthy enough and intact from scratching, sometimes with a closer observation, the fertilized female mite could be seen as a tiny brown triangular spot at the less scaly end of the burrow. The tiny brown triangular spot corresponds to the mouth part and anterior legs of the female mite (Fig. 2.1). The other end of the burrow, where the female mite started to burrow, is usually more scaly and whitish due to keratinization. The scales sometimes form a V-shape ("wake sign") (Fig. 2.6) [56].

For crusted scabies, confirmatory diagnosis could be easier compared to common scabies if suspected, and samples of the skin are taken. The samples could be taken from any affected skin lesions, and usually, a numerous number of mites can be observed under microscopy confirming diagnosis.

2.6 Treatment

Topical agents (e.g., 5% permethrin cream) are considered to constitute the first-line treatment, with oral ivermectin generally being reserved for recurrent, difficult-to-treat cases, or for patients with crusted scabies [28]. Both are neurotoxin for *Sarcoptes*. They can kill all mobile stages of the mites, but not the eggs [28, 57]. Eggs hatch in 3 to 4 days, and then become killable larvae. Therefore, the second application or administration must be given after hatching of the eggs, and no later than a fertilized female of the second generation starts laying eggs. Four to 8 days after the first application/administration is the optimal timeframe for the second dose [57]. Visible skin lesions may be very limited as there are delays in their development, and therefore, the treatment of the entire trunk and extremities, not only the visible lesions, is essential. The retro-auricular folds, the creases especially on the hands, feet, umbilicus, genitalia, and intertriginous areas such as axillae, inguinal regions, and natal cleft must not be overlooked during the treatment by a topical scabicide.

Resistance to scabicides is increasing throughout the recent years [58]. This constitutes a big challenge due to diverse symptoms of an infestation, the high healthcare cost, the possible complications, and the associated social stigmatization. The mites develop tolerance to the scabicides by a few known mechanisms including changing of their sodium or chloride channels where the scabicides bind allowing them to avoid hyperpolarization and paralysis, as well as increase in certain enzymes that catalyze the scabicides [58]. Further search for new drugs, or alternative control methods, to treat and prevent scabies is now becoming more an urgent need.

Topical steroids are effective for the itchy papules, by helping in alleviating inflammation. However, they can lead to immunosuppressed conditions for the unharmed and noninflamed skin, providing the most favorable conditions for *Sarcoptes* [33]. Increase in the number of *Sarcoptes* may be seen and puts an affected individual more at risk for transitioning to crusted scabies from common scabies. Topical steroids therefore should be avoided whenever possible. Furthermore as described earlier, scabies could be often misdiagnosed as noninfectious

inflammatory skin diseases, which require treatment with topical or oral steroids. When skin symptoms deteriorate with the use of steroids, scabies needs to be suspected and tested, and if with positive results, it needs to be discontinued immediately.

2.7 Management for Prevention of Further Spread

2.7.1 Prophylaxis

Prophylaxis is essential for all family members and close contacts (direct unprotected skin contact) with an infected individual (index case), who are at high risk of infection. This is especially because the signs of scabies may appear with some delays, reflecting the incubation time (14–30 days). They should be treated at the same time as the index case even in the absence of clinical signs.

2.7.2 Control Management

Scabies can show spread in any communities including institutional settings. Early detection and treatment of common scabies is crucial to prevent crusted scabies and its consequences. An individual affected by scabies should refrain from direct skin-to-skin contact during treatment. Transmission via fomites is reported to be unlikely [29, 35], but it is recommended not to share the items touched by the patient's skin directly, such as clothes, towels, linen, slippers and bed. Washing and cleaning can be performed as usual.

The scales shed from patients with crusted scabies contain many mites, and from these scales, further infestation to the nonscabies subjects may occur at a high rate. The patient with crusted scabies must be isolated and the personal protective equipment must be used. The room where an individual with crusted scabies stayed must be disinfected. Clothes and linen used by the affected individual should be washed in hot water at 60 °C temperature [29, 31, 59].

Considering that the disease can spread increasingly in the overcrowded areas, the items mentioned above must be carefully inspected at the time of diagnosis of crusted scabies in places such as prisons, soldier camps, refugee camps, residential care facilities for the elderlies and other conditions, and schools [60].

2.8 Conclusions

In this chapter, we have highlighted the updated knowledge on the biology of *Sarcoptes scabiei* var. *hominis* and its relevance to human scabies. For any infectious disease, it is essential that we understand about the causative agent, especially its biology, in understanding about the disease, and further in pursuing diagnosis, treatment, and prevention. Scabies provides us with an interesting opportunity for understanding this connection, as we can visualize the symptoms, and with the

recent invention of dermoscopy, we can also visualize the mites in the stratum corneum noninvasively. All knowledge gathered from the past and the present will form the basis for controlling scabies better in the future.

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Genetic Studies of *Sarcoptes scabiei*: New Tools for Old Questions

3

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3.1 Introduction

In the last two decades, genetic molecular tools offered to parasitologists and epidemiologists new opportunities to engage with old questions on the population structure of *Sarcoptes scabiei*. Among these, the main and oldest question is about the nature of *S. scabiei*: a single parasite species structured in host specific "variants" or something else and more complex (e.g., a cocktail of "strains" with different degrees of host specificity, in perennial evolution)? It is now undisputed that, thanks to contribution of molecular epidemiology, the second scenario has become the most accredited. The present chapter summarizes the recent literature (all together about 40 original articles specifically dedicated to *Sarcoptes* genetics) and illustrates which kind of answers and new questions have arisen. Of note, studies in wildlife mostly initiated in the frame of Conservation Medicine contexts have much contributed in the advancement of knowledge on the genetic variability of this iconic worldwide distributed skin pathogen.

3.2 Results Based on Sequencing of Internal Transcribed Spacer 2

The first contribution on *S. scabiei* genetics dates back to the very end of the past century. In a milestone paper, Zahler et al. [1] analyzed 23 pooled samples of mite isolates from nine host species in four continents, using the second internal

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transcribed spacer (ITS-2) of ribosomal DNA (rDNA) as genetic marker. Authors concluded that *S. scabiei* consists of a single, heterogeneous species. It was noted by Berrilli et al. [2] that the "monolithic" results obtained by Zahler et al. [1] were possibly related to the fact that their study was based on pooled samples and that genetic polymorphism among single individuals may thus have been underestimated. From here on, *S. scabiei* DNA has been obtained by individual mites only. However, the same view as Zahler et al. [1] was subsequently endorsed by Gu and Yang [3] who could not differentiate between sympatric and allopatric isolates from pigs and rabbits in China, nor between them and allopatric deposited sequences from humans and a range of other domestic and wild mammals. Actually, while ITS-2 has been widely appreciated by molecular taxonomists for distinguishing closely related species and examining phylogenetic relationships within parasitic Arachnida genera [4, 5], further studies clearly showed that ITS-2 is not suitable marker for genetic characterization within a mite species, including *S. scabiei* [6] and the related worldwide distributed genera, *Psoroptes* and *Chorioptes* [1, 7]. Accordingly, the use of ITS-2 as the sole marker in the study of *S. scabiei* genetics has been dismissed. Some papers have nevertheless been published in which ITS-2 was used in parallel with markers that were proved to be more informative [2, 8–12].

3.3 Results Based on Partial Sequencing of 16S and 12S Mitochondrial rRNA Genes

Similarly as ITS-2, other genetic markers in large use for the detection of genetic variation among closely related taxa were proved to be suboptimally informative on *S. scabiei* genetics, if not the source of epidemiologically inconsistent (hence confusing) results. The so far investigated partial sequences of the 16S and the 12S mitochondrial rRNA genes are undoubtedly among them. In a study by Berrilli et al. [2], the first marker identified: (1) a significant amount of genetic differentiation between red fox (*Vulpes vulpes*)-derived mites (originating from two populations in Italy and one in Spain), and (2) a substantial similarity between mites from two geographically isolated but also closely related host taxa, Northern chamois (*Rupicapra rupicapra*) from the Alps, Italy, and Southern chamois (*R. pyrenaica parva*) from the Cordillera Cantabrica, Spain. However, one of the fox-derived populations unexpectedly clustered with the two chamois-derived mite populations, the first of them sympatric (Alps) but the other one obviously allopatric. Sound working hypotheses based on epidemiological evidence of similarity or differentiation between *Sarcoptes* populations, as in Berrilli et al. [2], are essential prerequisites to infer on the accountability of the genetic markers, or of a cocktail of them. In another study on mites obtained from wombats, dogs, and humans in Australia [13], the use of a 326 bp fragment of the mitochondrial 12S rRNA gene did not result in any genetic differentiation between host populations. Authors concluded that this was consistent with the argument that overseas people and/or their dogs introduced to Australia the *S. scabiei* mites that further infected wombats and put a serious threat on their conservation. While the fore mentioned general conclusion was

endorsed by other studies using the same and/or other genetic markers [14–16], it is now clear that the polyphyletic associations found in that early study were rather based on short uninformative fragments of the single adopted marker. In the remaining literature, partial sequences of 12S mtDNA have not been used further, whereas 16S mtDNA appears as a complement to other preferred markers such as partial fragments of the Cytochrome Oxidase subunit I gene (*COI*) or microsatellites [8, 10, 12, 17]. In general, information provided by partial sequences of 16S mtDNA was insufficient to unambiguously highlight host or geographic-related differences, not even between obvious allopatric and zoologically far apart hosts, e.g., between cattle, sheep, and rabbit from Egypt vs. wallaby and dog from Australia and chimpanzee from Tanzania [8].

3.4 Results Based on Partial Sequencing of *Cytochrome Oxidase* Subunit I Gene

The analysis of sequences of the *cytochrome oxidase* subunit I (*COI*) gene was first used by Walton et al. [17], in parallel with microsatellite markers, to investigate the genetic epidemiology of *S. scabiei* in Northern Australia. According to their study, human-derived mites were grouped into three clades, one of them including also animal (mostly dog and wombat) derived mites. While results were encouraging on the potential of this marker, microsatellite data suggested a different and more coherent genetic structure, in which a wombat, two human, an allopatric dog, and a sympatric "dog plus wallaby" clades could be identified. Interestingly, all subsequent *COI*-based molecular epidemiological studies were consistent in revealing distinct clades of human-derived mites [8, 12, 18, 19], thus calling into question the hypothesis of panmixia for *S. scabiei* in humans. On the other hand, sequences from mites of domestic and wild animal origin rarely clustered according to their host preference, and were most often grouped in a single multihost clade of uncertain epidemiological meaning [8, 10–12, 19–21]. Nonetheless, *COI* has been proved the most informative among mitochondrial DNA markers [16].

In two recent studies [15, 16], the first of which also included the phylogenetic analysis of near full-length mitochondrial genomes of mites from Australian wildlife and from humans and dogs from Australia, Asia, and Europe [15], analysis of *COI* gene sequences gave strong support to the hypothesis that Australian native wildlife became exposed to *Sarcoptes* mites not earlier than a few centuries ago, following multiple *Sarcoptes* introductions most likely from dogs following colonizers from across the globe. This hypothesis of multiple introduction events has also been implicated in North American black bears [11] and in wild canids in Japan [22].

Intriguingly, the phylogenetic analysis of *COI* gene was used to explore the scientific substantiation of the widely accepted hypothesis [23, 24] that humans were the initial source of the animal—namely dog and possibly wild canid—contamination with *Sarcoptes*. The results were clearly not consistent with a human origin of *S. scabiei* mites in dogs and, on the contrary, did not exclude the opposite hypothesis of a spillover from dogs to humans [25].

3.5 Results Based on Microsatellite Markers

Microsatellites have shown to be among the most informative genetic tools available at the moment. Thanks to these markers it is possible (at least in wildlife or poorly human-manipulated contexts) to identify species- and origin-related *Sarcoptes* strains and find unambiguous answer to intriguing questions such as: "within a community of *Sarcoptes* sensitive species, who is infecting who?" or "may a selected host species be infected by several *Sarcoptes* strains under natural conditions?". Early microsatellite-based contributions date back to the late 1990s. It was the merit of Walton et al. [26] to molecularly prove, for the first time, that closely sympatric hosts may harbor *Sarcoptes* mites belonging to different populations. The model, now a renewed one, comprised remote native Australians communities and their dogs, both endemically infected by *S. scabiei*. More than 700 individual mites were characterized by using a panel of only three microsatellites. Results showed that gene flow between mite populations on human and dog hosts was extremely rare if any. The same results were confirmed in a later study [17] by characterizing remarkably less mites albeit with a higher number of microsatellites.

Elsewhere, microsatellite markers were initially used to differentiate between *S. scabiei* populations responsible for outbreaks in free-ranging herbivores and carnivores in Southern Europe [27]. The main studied populations were mites from sympatric Northern chamois (*R. rupicapra*) and red fox (*Vulpes vulpes*) in Northern Italy, and from a Southern chamois (*R. pyrenaica parva*) population in Northern Spain with no spatial or ecological connection with the former two. No gene flow was found between groups, suggesting the existence of both host- and origin-related lineages. In a subsequent microsatellite study on a larger number of mites ($N = 251$) obtained from ten wild hosts in three European countries, Rasero et al. [28] showed that mite populations were clustered into three main groups: herbivore-, omnivore-, and carnivore-derived populations, which for the purposes of the study should be intended as synonyms of ruminants, pigs (wild boars), and carnivores (canids, felids, and mustelids), respectively. The separation between these groups was better supported than the geographical separations; nevertheless, a kind of subclustering was detected within each of these three groups that separated mite populations according to the geographical origin. These findings demonstrated that *Sarcoptes* is not a single panmictic population, not even within each geographical location. "Host-taxon law" (HTL) was the term suggested to identify this major and somewhat expected transmission pattern. In a natural multihost system in Spain, Alasaad et al. [29] provided evidence of the temporal stability of the genetic structure of *S. scabiei* under the host-taxon law.

A subsequent study in Masai Mara, Kenya, revealed a second transmission pattern eventually associated to ecosystems including top predators such as lions (*Panthera leo*) and cheetahs (*Acinonyx jubatus*) and their respective favorite preys, all enzootically infected by *S. scabiei* [30]. Microsatellite genetic typing showed the following: (1) absence of gene flow between the herbivore (Thomson's gazelle and wildebeest, *Connochaetes taurinus*)-derived and the two carnivore (lion and cheetah)-derived mite populations; (2) similarity between lion- and wildebeest-derived mite populations, suggesting *S. scabiei* cross-infection from wildebeests (the favorite preys of

lions); and (3) greater complexity of cheetah-derived *Sarcoptes* population which included three different subpopulations. One of these was cheetah-private, one was similar to the wildebeest- and lion-derived mite population, and a third was similar to the mite population derived from Thomson's gazelles, the favorite preys of cheetahs in Masai Mara. This new and complementary pathway was denominated "prey-to-predator." Another multihost model in Spain included two herbivores (Southern chamois and red deer), wolves (*Canis lupus*), an efficient predator of both chamois and deers, and red fox, a mesocarnivore with a not specialized opportunistic diet [31]. The study highlighted a greater genetic diversity in wolf-derived mite population, the only one structured in two subpopulations, namely one similar to the single fox-derived mite population and a second one similar to the single herbivore-derived population. This study confirmed that potential prey (herbivore)-to-predator (wolf) mite cross-infection may have taken place between investigated host taxa and, in general, that "prey-to-predator transfer may modify the host-taxa relationship" [32].

More recently, a microsatellite study pointed toward a possible further transmission pattern of *S. scabiei* between herbivorous Japanese serows (*Capricornis crispus*) and omnivorous Caniformia mammals in Japan, though under very weak predator-prey relationships [33]. In more detail, while sympatric and not sympatric Caniformia- and wild boar-derived mite populations appeared well differentiated according to the "host-taxon law," a close genetic relationship was found between Caniformia- and serow-derived mite communities at several distant locations. Authors hypothesized that *S. scabiei*-naive serows initially became infected through direct (e.g., with a moribund sick individual) or indirect (environmental) contact with Caniformia during peak years of epizootic mange waves in the latter. Authors used the terms "cryptic" or "hidden" to stress how unexpected genetic relationships of *S. scabiei* populations, mirroring transmission webs locally deviating from previously reported ones, may exist among multihost systems worldwide.

Overall, the identification of at least three different *Sarcoptes* transmission patterns by means of microsatellite markers provided a great incentive for epidemiologists, specialists in conservation medicine and informed wildlife managers, to insist in molecularly characterizing all possible mite populations within unexplored multihost mange outbreak areas. Ideally, outcomes of genetic structure studies should drive the debate on possible control options.

Microsatellite typing has been also used to track the origin of *Sarcoptes* infection and/or its main local reservoirs in case of: (1) multiple host infections, including humans [34]; (2) legal disputes on traded wildlife, if infected before their export or after import [35]; and (3) emerging infections in alien species ([36]; Fig. 3.1). In Australia, the use of microsatellite markers allowed to explore the biology of scabies recurrence in patients under ivermectin treatment showing that reinfection was a far more common event than recrudescence after unsuccessful treatment [37]. Finally, microsatellite typing accredited the hypothesis that an initial sarcoptic mange outbreak in the endangered San Joaquin kit fox (*Vulpes macrotis mutica*) derived from spillover of mites from the common endemically infected red fox (though not from infected coyotes and domestic dogs), whereas a second (apparently) separate outbreak was primarily maintained by kit fox-to-kit fox mite transmission [38], suggesting the need for adjustment of the control strategy.

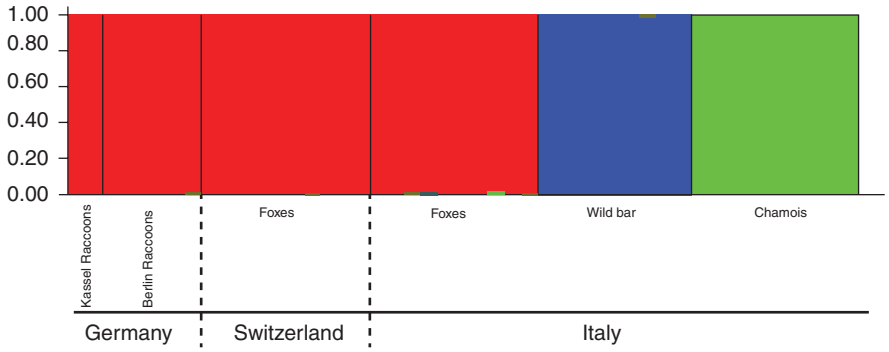

Fig. 3.1 Example of a bar plot [36] showing the stacked proportion of membership fraction of mite samples to each genetic cluster. Different colors represent the assignment likelihood of belonging to one of the clusters (red, blue, green). Vertical lines divide *Sarcoptes* host species and clarify the geographical origin of the samples. In this study, *Sarcoptes* mites from previously *Sarcoptes* naïve alien raccoons (*Procyon lotor*) and native red foxes in Germany clustered in the same population (red cluster) with a high proportion of membership fraction, suggesting that spill-over occurred to the detriment of raccoons under sympatric conditions. Mites from wild boars and Northern chamois were also included in the analysis. The population structure was computed with Bayesian model-based clustering using STRUCTURE 2.3.4 with admixture ancestry, and based on nine microsatellite loci (Sarms 33, 34, 36–38, 40, 41, 44, and 45). Twenty independent runs for each testing genetic clusters (*K*) values which ranged from 1 to 10 were performed with a burn-in period and Markov Chain Monte Carlo (MCMC) replicates of 100,000. The most likely number of clusters (*K*) was determined by considering the Delta *K* method described by [39] implemented in Structure Harvester

3.6 Results Based on Other Markers

To the best of our knowledge, two other markers have been explored in a single paper [20], namely segments of the glutathione-*S*-transferase class 1 (GST1) and voltage-sensitive sodium channel (VSSC) genes. Results were promising in characterizing pig-derived mites in Israel, though failed to highlight differences between mites of sympatric human, rabbits, and wild canids. The proteins encoded by the GST1 and VSSC genes were previously studied for immunogenicity and the role in acaricidal resistance, respectively, but further work is required to establish possible connections with *Sarcoptes* host preference.

3.7 Conclusion

Different markers have been used to investigate the genetic diversity of *Sarcoptes* mites. Among them, microsatellite markers proved suitable answer to questions arising in the context of clearly set epidemiological scenarios. Compared with microsatellites, ribosomal and mitochondrial markers were less able to reveal substructuring according to host and/or geographic origin within host groups.

Taken together, molecular data suggest that there is a substantial divergence between human-derived mite populations and other animal-associated mite populations. It is also clear from these data that human-derived *Sarcoptes* mites do not represent a single homogeneous (panmictic) population, and that the traditional concept of single host-related "variants" (*varietates*) is no longer adequate to embrace the epidemiological complexity of a global parasite with a uniquely wide host range.

In Europe, wild host-derived mite populations were found clustered into three main groups: herbivore-, carnivore-, and omnivore-derived *Sarcoptes* populations. Gene flow was revealed within, though not between groups. In parallel, a prey-to-predator pattern was revealed in Africa and Europe, in which top predators were found harboring different *Sarcoptes* subpopulations, including those deriving from their main preys.

Quite surprisingly, little knowledge has accumulated on the genetic diversity of *Sarcoptes* mites in domestic animals eventually related to difficulties in the collection of mites (e.g., due to frequent treatments and low parasitic densities compared with wildlife). Different clades seem to emerge in the case of dog, a relatively better investigated model globally. However, well-designed broad-based studies are needed on livestock and companion animals to drive control strategies, thus limiting animal welfare and economy issues, lowering the risk of zoonotic *Sarcoptes* infection in humans, and preventing the undesirable spillover of permissive *S. scabiei* strains toward wildlife.

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Host Immune Response to Scabies

4

Sara Taylor, Belinda Joy Hales, and Wayne Robert Thomas

4.1 Introduction

There is evidence that immune responses to scabies limit the extent of the infections while causing immunopathology, including the itch. They are also likely to differ in the different clinical presentations which have been broadly categorised as ordinary, which is by far the most common, nodular, bullous and crusted. Scabies has increased in prominence because of the increased use of immunosuppressive agents and acquired immune deficiency disease, frequent outbreaks in aged care institutions and now the spread through crowded refugee camps. It remains endemic in many tropical and subtropical communities such as India, South Africa, Panama and northern Australia where the prevalence of infection can be 20% and is associated with Group A *Streptococcus* infection, post-Streptococcal glomerulonephritis and rheumatic fever [1]. It has also become important because scabies induces IgE antibodies to antigens that cross react with homologues in house dust mite [2], not just confounding the diagnosis of allergic sensitisation, but doing so in regions where allergic disease is increasing due to changes from traditional lifestyles. A major problem has been the inability to culture scabies mites to obtain antigens for studying immune responses. This has been circumvented to some extent with the use of recombinant antigens and with the sequencing of scabies genomes to provide

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sequences of all potential antigens. Farm animals and wildlife are infected with variants of *Sarcoptes scabiei* providing economic and welfare reasons for research as well as sources of antigen and animal models. Pigs, dogs and rabbits have been used but the *S. scabiei* variants are host-specific necessitating continuing research into the infection of humans.

4.2 Immunity and Hypersensitivity

The high titres of antibody found to scabies antigens and the large number of antigens recognised by anti-scabies antibodies demonstrate that the infection elicits robust immune responses in keeping with the natural history of infection and its immunopathology. The regulatory mechanisms that underpin the responses and the effector functions however remain a mystery.

Studies of experimental infection [3] and clinical observations of naturally acquired scabies have reported valuable information. Infection begins with the transmission of a fertilised female that burrows into the stratum corneum, which is the outer keratinised non-living layer of the skin, where she lays eggs and deposits faeces and other material such as proteases to help produce the burrows [4] and complement inhibitors to ward off immune responses [5, 6]. In a process that takes about 3 weeks, larvae hatch and burrow up through the roof of the burrow onto the skin where they continue to burrow to create skin pouches. The new females are fertilised in the pouches to repeat the cycle, leaving the males to die as mating only occurs once in the lifecycle. Since a female can produce 3 eggs a day for 40 days and starts laying as soon as she burrows the scope for proliferation is enormous, but it doesn't happen. Instead, as shown by experimental infections of humans, the number of mites peak at only 50–350 and then rapidly declines over a 2- to 3-month period. Clinical infestations of scabies have been said to last for months if left untreated [7] although the documentation of this scant. Subjects presenting to clinics with the common form of scabies, called ordinary scabies, have on average a total burden of only 10–12 mites. These dynamics probably reflect a resistance phenomenon since experimental re-inoculation was found to only produce lasting infections in half of the volunteers and the burden of mites typically peaked at only 10–25. It was observed that the females began to produce burrows but soon disappeared from them, even when the infected areas were shielded from scratching. Where reinfection occurred it could last for at least 200 days which was the period of experimental observation. Reinfection after natural exposure has also been documented [3]. In a study of 886 cases in which the average parasite load was found to be 11.3 organisms, 45 cases of reinfection were found within 2 years of documented eradication. The average parasite burden was however only 3.2 indicating that resistance occurred even in the face of recurrence. Natural reinfection has been reported to occur in 27% of previously infected school children in Saudi Arabia [8] and for 50 out of 148 people in aged care facilities in Japan [9]. Dementia was a particular risk factor for the recurrence in the elderly [9] suggesting that aspects other than reduced immunity might be important although immunological functions of dementia patients have been reported to be diminished more than that expected for their age [10]. The high prevalence of crusted scabies in immunocompromised

subjects [11], where the mites proliferate profusely leading to populations of hundreds of thousands to millions in hyperkeratotic lesions, shows that although the protection is partial, a fully functional immune system typically controls the infection. Only about half of crusted scabies patients have patently impaired immune systems so the mechanisms of immunity might be both very specific and subtle and can be overwhelmed.

As well as the resistance to infection, immunological responses are central to the pathology and the severe itch found in scabies infections. Volunteers infected with scabies do not experience any discomfort or develop any skin symptoms until after a month of infection when oedematous lesions develop in the epidermis around the burrows, although not necessarily in close proximity to the mite. This is followed by erythema and an itch that persists even after the mite has been removed by treatment [3]. Intradermal skin tests with a scabies extract were found to induce a marked late-onset (24–36 h) and intensely itchy wheal and flare reactions but, perhaps contrary to expectation, this sensitivity only developed between 3 and 6 months after infection [3]. Later researchers have reported serum-transferrable immediate hypersensitivity reactions for patients tested within a year of scabies infection but not in subjects tested over a year after presentation [12]. Morgan et al. [13] observed similar skin test results for immediate responses to skin tests with scabies and house dust mite extracts with a high prevalence in patients with current scabies and a lower prevalence for previously infected subjects. In contrast to primary infections with scabies, volunteers reinfected with scabies showed erythematous lesions and intense itch within 24 h. The histopathology of the secondary scabies lesions showed monocytic perivascular inflammatory cell infiltrates indicative of delayed hypersensitivity [14].

Skin test studies for immunological hypersensitivity in animals that are naturally susceptible to variants of scabies have shown mixed results. Intradermal skin tests of pigs performed at different times after experimental infection showed they first developed delayed hypersensitivity then mixed immediate and delayed hypersensitivity followed by only immediate hypersensitivity [15]. Foxes developed immediate hypersensitivity reactions to a scabies extracts when tested 2 weeks after infection and maintained this type of hypersensitivity for up to 4 months after the clearance of mites. It was noted that they did not develop delayed reactions or protection to a second infection [16]. In contrast, reinfestation of dogs found marked resistance and, although skin tests with extracts were not performed, the skin inflammation of the reinfected dogs showed a large and prolonged infiltration of mononuclear cells peaking after 2 days and a large neutrophil response not seen in the primary infection [17]. Thus, although a degree of immunity appears to be produced as well as immediate and delayed hypersensitivity to scabies antigens, there are inconsistencies in the reports and a lack of corroboration.

4.3 Histopathology of Scabies Lesions

Scabies infection presents in many different ways but the spectrum of inflammation can be appreciated by considering the four types separately namely ordinary, nodular, bullous and crusted.

Ordinary scabies or the papulovesicular scabies is the most common form of infection presenting as a red intensely itchy rash of papules. Live mites, eggs and faeces are found in the outer layer of the epidermis and histological examination shows burrows along the stratum corneum with hyperkeratosis and increased thickness of the stratum granulosum (hypergranulosis) as well as vesicles. There are both diffuse and perivascular inflammatory infiltrates in the upper dermis consisting mainly of mononuclear cells. Eosinophils accumulate to a lesser degree but are found in most cases together with some neutrophils [14, 18]. T cells are very prominent in the infiltrates [19] and immunostaining has revealed a large number of macrophages, which from the expression of CD68 and lack of iNOS, are mostly of the M2 type [20]. Other features of the histology are that dermal infiltrates that are not in close proximity to the burrows are found and that there is a great deal of microhaemorrhage with thrombi and occasionally epidermal destruction and micro abscesses or pustules [18]. Plasma cells are detected in the lesions of about 20% of cases but in small numbers [18].

A less common form of infection is nodular scabies which presents as red-brown, extremely itchy nodules often located on male and female genitals but also in the axillae and abdomen. The histology shows dense perivascular infiltrates of lymphocytes with eosinophils, occasional plasma cells and monocytes [18, 21]. Like ordinary scabies most of the lymphocytes are T cells [19]. The degradation of the stratum corneum found with ordinary scabies is absent for nodular disease although there is intracellular oedema [21]. An historic characteristic feature has been the difficulty of detecting mites or burrows [7, 18] leading to view that the nodules were delayed hypersensitivity reactions directed to antigens persisting well after infection and indeed the treatment is often just with steroids. A rare histological finding of a mite that had burrowed through the epidermis and had become surrounded by dermal inflammatory cells has suggested this might be the cause, additionally explaining the prevalence of nodules on thin epidermal layers [22]. Contrary to these contentions other studies have found live mites and burrows [21] and the combined application of dermoscopy and histopathology has been reported to enable an almost 100% detection of mites and burrows [23]. Recent studies have even proposed that nodular lesions with readily detectable mites on the torso of infants, is the primary presentation of scabies for this age group [24]. Histological sections of post-scabies lesions have revealed a heavy perivascular lymphohistiocytic cell infiltration comprised of a non-Langerhans cell CDIa dendritic cells [25]. The high percentage of what are probably migratory inflammatory dendritic cells described for other skin lesions [26] clearly differentiates the post-scabies lesions from the dominant T-cell infiltration in nodular scabies.

Crusted or Norwegian scabies, which is the primary type of scabies found in immunosuppressed and immunodeficient people [11] differs markedly from the other forms of scabies by the absence of the usual itch [1] and the hyperproliferation of mites in the epidermis. The hyperkeratinisation of the skin and entrapment of body fluid as well as the mites, eggs, larvae and faeces form a crust that can be over a centimetre thick [27]. The epidermis has hyperplasia, spongiosis, vesiculation and neutrophilic microabscesses as well as thrombin deposits. The dermis has superfi-

cial and deep perivascular lymphohistiocytic infiltrate with numerous eosinophils, plasma cells and neutrophils [18, 28]. As examined in the two-case study of [29] most of the lymphohistiocytosis was from $CD8^+$ T cells with some CD4 cells. The subjects were a 27- and a 44-year-old indigenous Australians without overt immunodeficiency. Given the difference with the predominantly $CD4^+$ infiltrates found in ordinary and nodular scabies other crusted scabies patients warrant examination. One patient in a series of 11 cases of ordinary and nodular scabies however had a 1:1 CD4:CD8 ratio and another, an AIDS patient, had only $CD8^+$ cells [19], so the involvement of $CD8^+$ cells is not limited to indigenous Australians or crusted scabies.

Bullous scabies is a rare condition that presents with itchy large fluid-filled blisters that resemble bullous pemphigoid. It can develop concomitantly with ordinary scabies [30] or crusted scabies [31]. Although mites or their eggs and faeces are not found in close association with the blisters [31, 32], mites can be readily found on other parts of the body such as palm flexures or areas of skin with hyperkeratosis or papular rash, and the patients respond well to anti-scabies treatment. The histology shows diffuse and perivascular infiltration of eosinophils and neutrophils in the dermis similar to bullous pemphigoid. The deposits of complement C3 and immunoglobulin IgG in the basement membrane zone that are found in bullous pemphigoid have also been detected, but only in about a third of the subjects examined [30, 33, 34]. The presence of antibodies that bind to normal skin by immunohistology has, from the cases reviewed by Galvany et al. [34] and additional subjects not included in the tally [30, 35], been found in 30% of cases (7 out of 23). Western blotting which has been performed with skin extracts for three subjects [30, 33] showed antibody binding to several antigens known to reactive in bullous pemphigoid. It remains to be determined whether or not subjects without detectable autoantibodies have antibodies to scabies antigens or perhaps superinfecting microorganisms. Autoantibodies binding to transferrin, ferritin, lactoferrin, haptoglobin and albumin have been found in pigs infected with scabies [36, 37] and patients who once had scabies have been reported to be overrepresented in a wide number of autoimmune diseases [38] so it is possible that the tissue destruction or immunomodulation induced by scabies can induce autoimmunity.

4.4 T-Cell Responses in Human Scabies

The importance of cell-mediated immunity in scabies became apparent when subjects immunosuppressed for transplantation or as a side effect of anti-cancer chemotherapy began developing crusted scabies. The thousands to millions of mites found in the skin of these patients compared to the 10–12 mites found in ordinary scabies pointed to T-cell mediated protection. One of the diagnostic indicators sometimes used for crusted scabies is that their contacts have a high prevalence of ordinary scabies so the condition results from the host not the mite. The role of cell-mediated immunity was also evident in the first cases of crusted scabies described, which were in Norwegian lepromatous leprosy patients. Patients with this form of leprosy

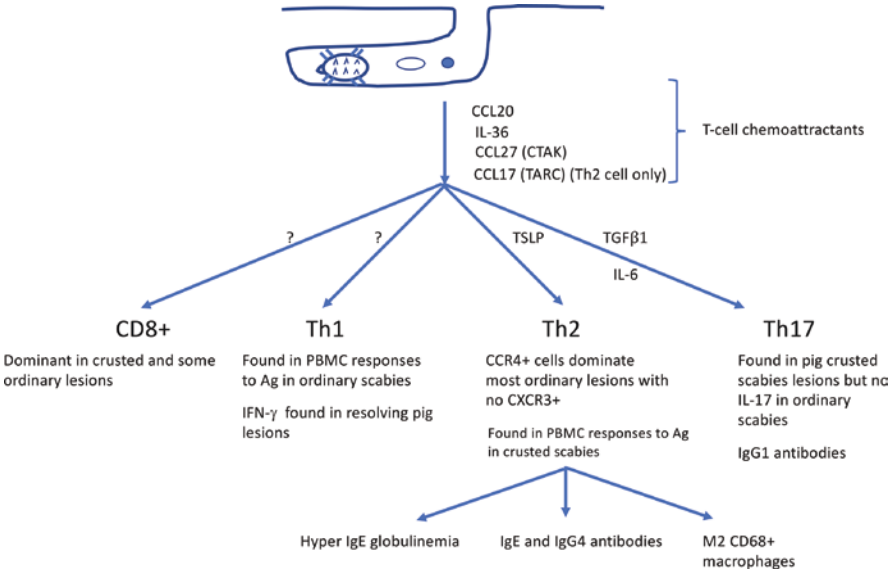

Fig. 4.1 T-cell responses in scabies: Diagram summarises known regulators and immunological consequences of T-cell immunity in scabies infection

have high bacterial burdens, poor delayed hypersensitivity responses to *Mycobacterium leprae* and are difficult to sensitise with experimental contact sensitising agents [39]. Since most crusted scabies patients do not suffer itch it is also possible this might be T-cell mediated as well as elements of the tissue damage. A summary of the evidence for the activation of different T-cell lineages and activities is shown in Fig. 4.1.

Scabies lesions show perivascular cuffing and dermal invasion of T cells and macrophages and the presence of eosinophils that would be typical of delayed hypersensitivity responses. In the case of ordinary scabies, the T cells were shown to be predominantly $CD4^+$ cells for most subjects but with some showing a higher presence of $CD8^+$ [19]. In contrast, the histology for two crusted scabies patients showed infiltrations of $CD8^+$ cells [29]. This is an important area for follow-up especially since the two crusted scabies subjects had normal profiles of T-cell subsets in their blood and normal values for other immunological markers. The $CD4^+$ cells in ordinary scabies were $CCR4^+$ with CCR4 being the receptor for the CCL17 (thymus- and activation-regulated chemokine, TARC) and CCL22 (macrophage-derived chemokine, MDC) which are chemoattractants for Th2 cells [20], and there was no staining for CXCR3 which would be found on Th1 and Th17 cells and no staining for IL-17. The $CD68^+$ M2 type macrophages also show a Th2 type response as well as the infiltrate of eosinophils. Noting that the sprouting of nerve fibres, that could be associated with itch, was no greater in scabies lesions than that found in non-itchy tick bites and that there was no infiltration of mast cells, Hashimito and colleagues [20] further reported that the M2 type macrophages were producing IL-31, a cytokine found to be responsible for producing itch in a number of diseases including skin lesions of psoriasis and bullous pemphigoid [40]. *In vitro* experiments

performed with mouse macrophages showed the IL-31 production was likely to be caused by exposure to the chemokine thymic stromal lymphopoietin (TSLP) produced by damage to the epithelium [20] and periostin, a pleotropic extracellular matrix protein induced in epithelia by the Th2 cytokines IL-4 and IL-13. TSLP, TARC and periostin are produced in increased quantity in scabies lesions [20]. TSLP itself and IL-33 which would be produced from damaged skin cells can also both induce itch [41] so the relative contributions need to be explored and other pathways cannot be excluded. TSLP which induces the maturation of Th2 cells, periostin and TGF-beta might be a major amplifier of the cascade [42, 43]. Th17 cells can express CCR4 but need CCR6 to respond to the attractant CCL20 to migrate to skin lesions such as psoriasis [44] where they are sustained and stimulated by IL-23 to produce IL-17, which causes tissue damage and inflammation. Although ordinary scabies lesions have not revealed a significant increase of IL-17 [20] there are insufficient data to know if that is case for all manifestations of scabies infection.

Although CCR4 is predominantly found on $CD4^+$ cells it is found on a sub-set of human memory $CD8^+$ which respond to the chemoattractant activity of the Th2 associated TSLP and MDC chemokine. As reported for the population in the blood, these cells produce both Th1 and Th2 chemokines [45]. Infiltration of $CCR4^+$ $CD8^+$ cells into chemically induced skin inflammation has been described [46], but without a description of their cytokine production, and it has been reported that psoriasis patients have an increased number of Th2-type CCR4 $CD8^+$ cells in their blood [47]. While $CD8^+$ cells play a key part in the pathogenesis of psoriasis and related skin disease, IL-17 is implicated in the pathogenesis of these conditions [48] and the trafficking chemokine receptor found in the lesions is CCR5 so the $CCR4^+$ $CD8^+$ cells could be regulatory. Certainly $CD8^+$ infiltrations of the dermis in skin disease need more exploration especially given their abundance in crusted scabies lesions.

Further phenotyping of the T cells in ordinary scabies lesions, made in the context of distinguishing scabies lesions from malignancy, demonstrated the presence of abundant CD30-positive T cells. The CD30 antigen, well-known for its presence on the Reed Sternberg cells of Hodgkin lymphoma, is found in many tumours and is under investigation for interactions that modulate anti-tumour responses. It is expressed by 1% or less of $CD4^+$ and $CD8^+$ cells in the blood of healthy humans but can be upregulated on nearly all of them by T-cell receptor engagement [49]. It was initially thought to be a marker for activated Th2 cells but is now known to be expressed by T cells making Th1 and Th2 responses [50]. More recently important CD30–CD30L interactions in Th17 responses as well the regulation CCR6 required for skin migration have been noted [51, 52]. The mechanisms and outcomes are however still very much the subject of investigation with up and down regulatory effects being seen depending on the cell types expressing the CD30 and the participation of soluble CD30. Despite an upregulatory function for CD30 in the induction of Th17 cells, CD30 knockout mice have heightened Th17 responses in the mouse model of imiquimod-induced psoriasis due to the ablation of $CD30^+$ gamma-delta T cells [51]. Gallardo [19] noted that CD30 expression wasn't found in scabies lesions existing for less than 3 months. There was in fact only one such subject so more observations are required and in general time courses for T-cell infiltration of scabies lesions have not

been documented. Most studies do not define the age of the lesions, which would probably be difficult and inaccurate. Studies of dogs have shown that T-cell infiltrations peak after a month of experimental infection [53] but this used an inoculum of 3000 mites and $CD4^+$ cells were only abundant in reinfected dogs [54]. The cases described by Gallardo et al. [19] corroborated an earlier single case of a CD30 infiltrate of a scabies nodule also thought to be lymphomatoid papulosis [55].

In vitro antigen-induced peripheral blood T-cell stimulations have been examined in ordinary and crusted scabies patients [56]. Proliferative responses were found to a cysteine protease antigen with cells from 40% to 60% of crusted and ordinary scabies patients responding compared to 20% of non-scabies exposed controls. A similar prevalence of responsiveness was found for a high IgE-inducing apolipoprotein antigen, although 30% of the non-exposed controls responded. Lesser but significant proliferative responses were found to an inactive cysteine protease paralogue and a serine protease. When the mean size of the responses was considered, crusted scabies patients had significant responses to all the antigens as compared to unexposed controls but there were no significant differences when compared to ordinary scabies and scabies exposed subjects, which in turn were not significantly different to the unexposed controls. Cytokine responses were measured to the apolipophorin and cysteine protease antigens that not only induced the highest proliferative responses but also bound serum IgG4 and IgE antibodies. A Th1 type response was evident for ordinary scabies patients to the cysteine protease antigen who showed higher release of IFN-γ compared to that found for unexposed controls and insignificant IL-4 and IL-5. Crusted scabies patients in contrast had increased IL-5 but not IFN-γ responses compared to the unexposed controls. This suggested a more Th2 biased response for the crusted scabies but when directly compared there were no significant differences between the crusted and ordinary scabies groups. The only significant difference found for all the comparisons with the apolipoprotein antigen was increased IL-13 (but not IL-4 or IL-5) in crusted scabies compared to unexposed controls. IL-10 which can downmodulate immune responses was not induced by either antigen for crusted or ordinary scabies patients. In addition, immunohistochemistry of the lesions of two crusted scabies patients did not find IL-10 [29], also suggesting it might not be involved. A similar result was found for in vitro peripheral blood monocyte stimulation assays with a scabies extract in which IL-10 was induced for both normal and alleged scabies sensitised subjects [57]. Most of the sensitised subjects were people occupationally exposed to dog scabies, so were not necessarily infected. Abd El-Aal et al. [58] however did find more IL-10 in the serum of scabies patients and reported that it was associated with reduced clinical manifestation and reduced IgG and IgE as well as reduced serum IFN-γ.

4.5 T-Cell Responses in Animal Scabies

Cytokine production has been experimentally examined in pigs infected with *Sarcoptes scabiei* var. *suis*. This natural pathogen of pigs can infect humans causing itchy papular rashes but cannot sustain its lifecycle [59]. Using the

immunosuppressive corticosteroid dexamethasone to enhance the infection in some animals, it was found that infected pigs, regardless of their clinical outcome, showed early elevated numbers of peripheral blood IFN-γ-secreting $CD4^+$ T cells and gamma-delta T cells evident before the development of symptoms [60]. When the blood responses and lesions were examined after 15 weeks, the skin cell infiltrates from pigs with crusted scabies had significantly higher numbers of $CD8^+$, gamma-delta and IL-17 staining T cell than those with ordinary scabies which in turn were higher than uninfected controls. Peripheral IL-17 levels were not increased, suggesting that IL-17 secreting T cells were localised to the skin. Both crusted and ordinary scabies groups had significant skin infiltrates of IFN-γ producing T cells with the crusted group being higher than the ordinary scabies. A follow-up with gene expression analysis to address a wider range of cytokines and a time course of lesion development showed responses were evident from 4 weeks which was the first time point of observation [61]. Pigs that developed crusted scabies, whether or not they had been given dexamethasone, showed the transcription for the Th2 cytokines IL-4 and IL-13, and the Th17 cytokines IL-17 and IL-23. Immunohistochemistry showed IL-17 production by inflammatory dermal cells with diffuse staining of keratinocytes. Pigs that did not receive immunosuppressive treatment and only developed transient infections showed a strong lesional transcription of IFN-γ reflecting earlier findings. Noting that dexamethasone treatment is a common antecedent to the development of crusted scabies in humans these results provide intriguing insight for further study. As clearly seen with contact sensitising agents the dose of initial exposure is critical for the development of hypersensitivity [62] so the events seen after the application of 2000 mites, as used in the model, might differ from infections generated by a single fertilised female.

Cytokine production measured by immunohistological staining of skin lesions of dogs naturally infected by cohabitation with scabies infected cage-mates [63] showed that the Th2 cytokines IL-4 and IL-13 and Th17 cytokine IL-17 were detected in lesions examined 2 weeks after exposure but not after 1 week. IFN-γ was not examined. The inflammatory cells and epidermal tunnels were not detected until week two but it is not precisely known when the infection occurred. The cytokine levels remained at about the same level for a 7-week observation period with a decline in the tunnelling at 6 weeks. Cutaneous neutrophils, macrophages, lymphocytes and eosinophil were present at week 2 and remained at varying levels during the entire observation period. Plasma cells were not detected.

4.6 Spectrum of T-Cell Responses in the Skin

Th17 responses are important components of immune-mediated inflammatory responses in many tissues of the body and have received much attention for skin disease. Psoriasis, which is a common hyperkeratotic inflammatory disease of probable autoimmune origin, is marked by a combined Th1 and Th17 skin lesion. Inhibiting the Th17 response, which is orchestrated by IL-23 produced by antigen-presenting cells and mediated by T cells producing IL-17, IL-21 and IL-22, has

shown considerable clinical efficacy for treating human disease [64]. Atopic dermatitis, a common skin disease associated with allergy, produces combined Th2 and Th17 inflammatory lesions [64], but here anti-Th17 strategies have failed to modify disease, suggesting it secondary to the initial pathology. Counter to this, increased expression of Th17 and Th2 genes in non-lesional skin of atopic dermatitis patients suggests an early involvement [65] especially since IL-36, a central cytokine in the Th17-induced inflammatory cascade of psoriasis, was also upregulated.

Studies of mice have shown that exposure to experimental antigens via the skin can produce several types of strong immune responses. The epicutaneous application of protein is known for the induction of Th2 and Th17 immune responses with high titres of IgE antibodies [66, 67] and IL-17 [68]. IgG antibodies can be detected; however, intradermal injection of antigen, which might resemble scabies tunnels or their contents reaching down to the dermis, induces high titres of IgG antibody without adjuvant and inhibits Th2 IgE responses [69]. The balance of Th1, Th2 and Th17 responses to epicutaneously-applied contact sensitising agents varies greatly from sensitiser to sensitiser and between protocols possibly reflecting the differences in innate cytokine release [70]. Once touted to induce Th1 immunity, the commonly used contact sensitisers dinitrofluorobenzene, trinitrochlorobenzene and oxazolone are now known to elicit mixtures of Th1, Th2 and Th17 responses that can be mediated by $CD4^+$ and $CD8^+$ cells. Fluorescein isothiocyanate, at least when applied with dibutylphthalate, elicits a Th2 response with skin infiltrates of Th2 cells and eosinophils. It not unexpected induces high titres of IgE antibody but so does the repeated application of trinitrochlorobenzene [71, 72] and oxazolone [71, 73], with the continued applications inducing the replacement of an initial Th1-biased response to one biased to Th2 [74]. A further study has shown that the continued application induces three waves, Th1, Th2 and Th17 with each one possibly inhibiting the preceding one [75]. The increase in IgE responses was selective in that IgG antibody production diminished with continued antigen exposure [76] and, unlike responses to proteins injected with alum, the IgE increased with increasing doses of sensitiser and waned without continued application. IL-31 which is usually associated with Th2 cells has been shown to mediate itch reactions to contact hypersensitivity to both the Th1 biased dinitrofluorobenzene and Th2 type sensitiser fluorescein isothiocyanate [77]. These studies not only show skin responses can vary with changes in antigen presentation but also the need to study the sequential changes that occur over extended time periods.

4.7 Innate Cytokines and Chemokines

A key aspect of responses induced via the skin is the induction of epithelial cell chemokines TSLP, IL-33 and IL-25 by tissue damage and danger signals. TSLP and IL-33 induce Th2 responses while IL-25 has broader activity and has been shown to important Th17 responses [41]. Another central chemokine for skin responses is CCL27 (originally cutaneous T-cell attracting chemokine, CTACK) produced by keratinocytes. It has been found to be induced by scabies burrowing into artificial

skin constructs [78] and is expressed in high amounts in the skin of patients with psoriasis and atopic dermatitis [79]. It is a potent chemoattractant for skin homing T cells acting via the CCR10 receptor. It is not restricted to $CD4^+$ T cells being able to direct the trafficking of CD8 [80] and innate lymphoid cells [81] and has been proposed to regulate the balance of effector and regulatory T cell during tissue homeostasis [82]. The artificial skin organ culture model of Morgan and colleagues showed that burrowing by scabies up-regulated not only the secretion of the skin chemoattractant CCL27 but many other pro-inflammatory chemokines and cytokines demonstrated for TSLP, IL-1a, IL-1b, IL-1ra, IL-6, IL-8, MCP-1, G-CSF, GM-CSF and M-CSF [78]. The secretion of the interleukin 1 receptor antagonist (IL-1ra) indicates, as proposed by Morgan et al., that its anti-inflammatory responses might be protective. IL-1a is produced in very high quantities in the skin in response to many cytokines including IL-1 and GM-CSF and to microbial products and tissue damage [83] so it probably has a key function in preventing exaggerated inflammatory responses. A follow up of the in vitro skin invasion model used a global gene expression assay to show a more than twofold upregulation of 128 genes [84]. The most stimulated cytokine gene was interleukin-36 gamma previously known as interleukin-1 family member 9 (IL1F9). It is part of an IL-1-like sub-family critical for skin immunology and IL-36 gamma produced by keratinocytes is central to the IL-23-Th17 axis in psoriasis activating Th1 and Th17 cells [85]. It is also overexpressed in atopic dermatitis [65]. Other highly upregulated genes were for IL-1B, IL-1A, the IL-1 receptor, GM-CSF, the IL-23 receptor and lymphocyte chemotactic protein CCL20. CCL20 is weakly chemotactic for neutrophils and strongly chemotactic for lymphocytes noted for attracting Th17-type $CCR6^+$ cells to skin lesions in psoriasis [44]. High levels of IL-1 can further enhance Th17 differentiation by the decreasing regulatory T cells that are co-induced by TGF-beta produced during the initiation of Th17 responses [86]. The Th2 inducing chemokines TARC and MDC have been shown to be present in high amounts in ordinary scabies lesions [20] but that study did not examine early events. Walton et al. studying two crusted scabies patients similarly showed strong immunohistochemical staining for TGF-beta1 as well as IL-1B [29], but the production of TGF-beta1, important for Th17 responses, has not been reported in ordinary scabies lesions or in response to burrowing. The crusted scabies lesions also did not show TNF which is important in Th1, Th2 and Th17 immune responses or the immunoregulatory IL-10 or the IL-1R antagonist.

4.8 Antibody and Immunoglobulin Responses to Scabies

Scabies mites ingest host immunoglobulin as evidenced by its detection in the gut and oesophagus of mite freshly removed from the host [87] and IgE has been found in the gut and mite burrows by immunostaining tissue sections [56]. The mites would accordingly have internal as well as external exposure to antibodies in the fluid that seeps into the stratum corneum. Studies with the injection of human serum into mice have shown slow, 12-h, seepage into the stratum corneum which was increased if the serum was from pemphigoid patients with autoantibodies [88].

Complement deposition is also found in the gut of the scabies in tissue section as well as on the surface of the mites and the burrow lining [89] suggestive of antibody binding, and complement deposits have been found in tissue sections near mites indicating antibody complexes with released mite antigens [90, 91]. Scabies mites have evolved to produce a large multi-gene family of inactive serine proteases [92] that can be found in the gut [93]. At least one of their functions appears to be as potent inhibitors of complement activation [93, 94] and as such could be critical for protecting the mites from antibody mediated immunity. Scabies also produces a serpin that inhibits complement activation and the attraction of neutrophils [6].

The early indications of antibody responses to scabies were that half of infected patients had increased levels of serum IgG and IgE immunoglobulins that decreased after successful eradication of the parasite [95]. The likelihood that the IgE included specific antibodies was indicated by the disproportionate number of scabies infected subjects that were positive for IgE antibodies to the common house dust mite, *Dermatophagoides pteronyssinus* [96]. Both the serum IgE immunoglobulin levels and the IgE antibodies to *D. pteronyssinus* decreased after 12 months of anti-scabies treatment [97]. Chevrant-Breto et al. similarly found about half of scabies patients had elevated IgE immunoglobulin levels and further reported that the levels were proportional to the severity of the skin lesions [98]. A Swedish study also found elevated IgE immunoglobulin levels with 10,000 IU/mL being reported for a crusted scabies patient [99]. The high IgE immunoglobulin levels found in crusted scabies subjects has been a consistent feature across many different geographical regions [11].

Direct testing with a scabies extract showed that an intracutaneous injection produced immediate hypersensitivity reactions in subjects infected with scabies for less than 1 year. It was transferable to a normal subject with serum indicating it was IgE antibody but it should be noted that skin prick tests, as used for standard allergy testing, were negative and subjects infected for over a year showed no reactivity [12]. The poor performance of the skin prick tests could well be due to difficulty in preparing scabies extracts from human infections. Measurements with an extract made from the more readily obtainable pig variant of *Sarcoptes scabiei* showed IgE antibodies in 50% of subjects tested by the radioallergosorbent assay including in subjects without IgE antibody binding to house dust mite extract [99]. Dahl et al. similarly found IgE antibodies to pig scabies extract in 30% of subjects tested, finding no correlation of the titres with itch [100], which would be consistent with the itch being mediated by T cells.

A more recent study of IgE antibodies, which used extracts of the storage mite *Acarus siro* and the house dust mite as surrogate antigens, has provided a better analysis by using the more quantitative propriety ImmunoCap assay [101]. There were increased IgE immunoglobulin levels in 80% of the patients and, varying with the mite species used, 30% to 50% IgE antibody positivity and 45% to 60% skin prick test reactivity. The IgE immunoglobulin levels were extremely high for patients with severe infection typically being over 1000 IU/mL with the mild and moderate group being under 250 IU/mL. Since severe was defined having over 50% skin involvement and moderate as over 20% the patients must have had extensive

infections. The antibodies titres found to the extracts were mostly in a range similar to that expected for asthmatics allergic to house dust mites, thus showing a high level of cross-reaction. The relationship of the cross-reactivities with the severity of infection was not given but the levels of IgE immunoglobulin did not correlate with serum eosinophil cationic protein as found for Th2 type allergic disease. Remarkably large decreases in IgE and the cationic protein were found only 6 weeks after anti-scabies treatment with permethrin.

A study of ordinary scabies in North America found low or moderate levels of IgE immunoglobulin and a 60% prevalence of positive skin prick and radioallergosorbent tests with extracts from a canine variant of scabies [13]. There was little diminution of the IgE immunoglobulin or antibodies when patients were retested 6–10 weeks after anti-scabies treatment. IgE immunoglobulin did eventually return to normal but half the subjects were positive to skin prick tests with house dust mite extract and 20% were positive by the radioimmunosorbent test. Western blotting for IgE and IgG antibodies to scabies in this study showed weak binding for most patients which was limited to 1–2 bands that varied from patient to patient. A later study that included crusted scabies patients, showed that IgE antibodies from crusted scabies patients strongly bound many bands while IgE from ordinary scabies had limited reactivity [102]. The highly staining bands were found across a 20–220-plus kDa range and did not necessarily bind IgG. This could be because western blotting with IgE is usually more sensitive than with IgG due to the low IgE immunoglobulin background. The IgE antibody binding was only found in three out of seven ordinary scabies patients and the IgG antibody in two. It was weak and limited to 1–2 bands. The pattern of IgG antibody binding for both crusted and ordinary scabies varied from patient to patient with no dominant reactivity. A study of IgG antibody using fox variant scabies for the antigen showed antibodies were detected in half of subjects which increased with the severity of disease [103]. Subjects with severe lesions and crust were nearly all positive with high levels of reactivity. There was a weak correlation with the length of time of the infection which also correlated with the severity noting that subjects could produce high levels of antibody by 6 weeks and clear positives were evident after two. There was no change in the IgG antibody after 12 weeks of treatment. A further study of IgG antibody conducted with an undefined scabies extract showed that ordinary scabies patients had binding that increased with increasing IgE immunoglobulin levels and serum IL-6 indicating a correlation with active and more severe disease [58].

Antibodies to specific antigens have also been investigated, firstly using recombinant glutathione-*S*-transferase [104]. It bound IgE and IgG4 from half the crusted scabies patients tested but had almost no binding with antibodies from ordinary scabies patients or from previously infected subjects. There was also no IgE or IgG4 binding to a helminthic glutathione-*S*-transferase which, since the disease was conducted in area noted for helminthic disease, would indicate specificity. Total IgG antibodies however bound equally to the helminth antigen and although controls had lower reactivity they were urban dwellers expected to have less exposure to parasites. Further studies with recombinant antigens examined responses to a cysteine protease, an inactive cysteine protease paralogue, a serine protease and a type

II/I apolipophorin [56]. IgE binding to the apolipophorin, the cysteine protease and the cysteine protease-like antigen was higher with sera from crusted scabies patients compared to sera from ordinary scabies patients, especially for the apolipophorin. The IgE binding to the cysteine protease and the apolipophorin antigens was higher with sera from ordinary scabies patients compared to sera from subjects with previous exposure. IgG4 antibodies to the apolipophorin were similarly higher in crusted scabies patients compared to ordinary scabies and higher in ordinary scabies compared to unexposed controls. IgG4 binding to the cysteine protease and the inactive protease was also elevated. Only slight or no differences between control and patient groups were found for the other antigens and for total IgG, IgG1, IgM and IgA antibodies. The interpretation of these results needs to consider that none of the recombinant antigens were produced in way that would recapitulate the structure of their natural counterparts. Further study of the apolipophorin antigen showed extremely high levels of IgE antibodies for crusted scabies, 100–700 IU/mL, very high levels for ordinary scabies and slightly elevated levels for previously infected subjects [105]. There was only low-level cross-reactivity with the homologous apolipophorin of house dust mite, which has an overall amino acid sequence identity of 60%. Examination of experimentally infected pigs that developed crusted scabies also showed good diagnostic potential for this antigen [106]. Antibody responses of ordinary scabies patients have been measured with two other recombinant antigens [107]. IgE binding to tropomyosin, an antigen that is readily produced as a well-folded antigenic recombinant molecule [108], showed little antibody binding but paramyosin, as demonstrated with recombinant peptides, showed higher levels of IgE binding with sera from scabies than controls and house dust mite allergic subjects.

4.9 Scabies and House Dust Mite Cross-Reactivity

Many of the earliest observations of immune responses to scabies showed IgE antibody binding and skin test reactions to extracts of house dust mites. Studies with recombinant scabies proteins have begun to define the antigens responsible for this and the degree of cross-reactivity. Scabies and house dust mites are in fact phylogenetically disparate with most homologous proteins showing only 20% to 30% sequence identity. For most proteins, 50% to 70% sequence identity is required for cross-reactivity [109], and this is not typically found between scabies and house dust mites. There are some proteins that do have sufficiently conserved structures but it needs to be appreciated that most of the IgE antibody responses induced by house dust mites in allergic disease is directed to a small number of proteins most of which have little identity with scabies homologues. Sera from patients with crusted and ordinary scabies and subjects with previous scabies exposure have shown negligible IgE binding to the Der p 1, 2, 5, 7 and 8 allergens of *Dermatophagoides pteronyssinus* [2]. Since Der p 1 and 2 are by far the most serodominant house dust mite allergens and Der p 5 and 7 are important mid-tier allergens [110, 111] used in allergen chip microarrays [112] their IgE reactivity clearly

distinguishes house mite allergy from scabies infection. Conversely IgE antibodies in about half the sera from scabies infected subjects bound the amylase allergen Der p 4 and the arginine kinase allergen Der p 20. Crusted scabies patients had very high titres, reaching 500 IU/mL. The binding of ordinary scabies subjects, although less, was of similar magnitude to the responses of house dust mite allergic subjects to their dominant allergens but was mostly confined to the amylase. Sera from previously exposed subjects did not have elevated IgE titres to Der p 20 and only had low and infrequent reactivity to Der p 4. Arginine kinase, which is the arthropod equivalent of creatine kinase, is one of the most abundant proteins found in house dust mite extracts [113] so the IgE binding to this component could make a large contribution to the observed cross-reactivities of extracts. House dust mite allergic subjects have infrequent low-titre IgE binding to Der p 20 [114] so, along with the lack of reactivity to immunodominant house dust mite allergens, the high levels of antibodies found in scabies patients provides a very useful marker for distinguishing scabies infection from allergy. A study of the arginine kinase of *D. farinae* showed that it only produced borderline, 3 mm, skin prick test reactions in 3 out of 17 patients [115], and there was insufficient information to exclude scabies infection or other cross-reactivities.

Walton et al. also showed that sera from scabies patients did not bind to house dust mite tropomyosin (Der p 10) or to fragments of the apolipophorin Der p 14, which included the previously unstudied N-terminal 260 amino acids of this large protein. These observations are consistent with reported studies with scabies proteins [105, 107] showing low binding to scabies tropomyosin and strong but largely non-cross-reactive binding to the apolipophorin peptides.

Different to their IgE reactivities, scabies infected people had IgG1 antibodies to all the mite allergens examined especially Der p 4, 10, 14 and 20. The median titres were about 25 μg/mL, which are about 5 times higher than those found to the immunodominant allergens in house mite allergic subjects [114] and similar to those found after bacterial and virus infections and for human vaccine responses [116]. IgG4 antibody responses were not as frequent but subjects with crusted scabies had higher titres of IgG4 antibody binding to Der p 20 compared to Der p 1. These cross-reactivity studies immediately explained the unusual results found in a previous study of indigenous Australians in a tropical community [117]. Their pattern of allergen binding, with high titres of IgE to Der p 4 and Der p 20 with low titres to the immunodominant allergens, mirrored those found in people previously infected with scabies as did their pattern of widespread IgG1 binding and infrequent IgG4 binding. This population was studied because the subjects were known to have high IgE binding to house dust mite extract but had little allergic respiratory disease.

The results not only show the benefit of testing with Der p 4 and Der p 20 to discriminate scabies infection from house dust mite allergy but, because of the use of standardised assays, provide minimal estimates of absolute concentrations showing the large amount of IgE and IgG antibody elicited by scabies. Foremost amongst future studies should be the examination of responses to Der p 11 (paramyosin) and Der p 14 (Class II/I apolipoprotein) using recombinant allergens with authentic structures instead of the fragments used to date. Antibody binding to the homologue

of the peritrophin allergen, Der p 23, would be another priority. It has been identified as binding IgE from the sera of house dust mite allergic patients at high frequency, probably accounting for IgE responses in subjects with little response to the group 1 and 2 allergens [118]. Amylase binding in particular needs further study because the genome sequence of *Sarcoptes scabiei* shows that it does not have an alpha amylase gene [119]. The induction of anti-amylase antibodies has been corroborated in experimentally infected pigs [120] and the high titres make cross-reactivity with a distantly related protein unlikely so an explanation is required. Possibilities are that the binding could be to carbohydrate since natural Der p 4 was used as the antigen or the amylase was produced by a symbiotic microorganism. Also since the antibodies in pigs could be detected with bacterial and blow fly amylases it might be due to infestation of the skin lesions.

4.10 Recombinant Antigens

Since scabies are obligate parasites it difficult to obtain sufficient mites to conduct assays with extracts let alone purify antigens. *Sarcoptes scabiei* variants from dogs, foxes, pigs and rabbits have been used to make extracts but they do have differences reflected by their ability to grow in different hosts. The difference in amino acid sequences between pig, dog and human scabies variants has been analysed for the family of inactive cysteine proteases paralogues [121]. The homologous proteins of the type c and e family members were about 95% identical between the species and because of this would be expected to show considerable antibody cross-reactivity. The pig and human type a homologues had over 90% identity with each other but only 75% to the dog homologue, which by analogy with comparisons of different species of house dust mite, would result in significant antigenic differences. The type b homologues of dogs and humans were almost identical but were less than 90% identical to the pig. Of possible greater concern is the restriction of the type d homologue to humans and the restriction of the type e homologue to pigs and dogs.

Another large problem is that studies with extracts not only mask the importance of responses to different components but the extracts are likely to be highly variable in composition, as found for house dust mites. Many of these are devoid of important antigens and have varying quantities of immunodominant components [122]. For scabies, the antigens in the eggs, faeces and other components deposited in the tunnels should not be missed. Knowledge of antigens is also needed to produce peptides for T-cell and epitope studies although this can now be done with the genome sequence [119].

Immunoscreening of recombinant cDNA expression libraries has discovered the apolipophorin/vitellogenin like antigen [123], peritrophin [89], paramyosin [124] and the MADF antigen [125] and cDNA cloning and prior knowledge identified glutathione transferase, cysteine protease, serine protease, an inactive paralogue of cystine protease and paramyosin as antigens of interest [126]. The cross-reactivity with house dust mite has identified arginine kinase as an antigen [2] and pointed to the possibility of a protein cross-reactive with amylase. Scabies arginine kinase had

87% amino acid sequence identity with Der p 20 from the house dust mite so the serology with the house dust mite homologue gives a good measure of its high antigenicity. A combined proteomic and molecular cloning strategy identified ferritin as an IgG binding entity in 16% of subjects [127] and while this strategy identified other proteins that bound even more IgG, they had high reactivity to IgG from uninfected subjects. The 2-D immunoblot screened for IgG and IgM binding in this proteomic study showed the highest immunostaining to spots containing dehydrogenase/reductase SDR family member 2-like protein, a short-chain alcohol dehydrogenase-like protein, proteasome sub-unit beta type-4-like protein, fumarylacetoacetase-like protein, actin-interacting protein 1-like protein and heat shock protein 70-like protein. There was also binding to the apolipophorin/vitellogenin like and arginine kinase antigens.

A list of molecularly defined antigens is given in Table 4.1. From studies conducted to date, the type II/I apolipophorin which is classified as a large lipid binding protein and probably doubles as vitellogenin in the eggs is highly antigenic and has demonstrated utility. There is also evidence for the high allergenicity of arginine kinase and paramyosin. Proteins that have shown lesser activity are a glutathione-*S*-transferase, a cysteine protease, an inactive paralogue of cysteine protease, a serine protease and ferritin. A protein of unknown function, designated MADF, has been shown to be antigenic for scabies-infected dogs and is interesting because it could be readily found deposited in scabies burrows. Other interesting proteins that have described are a peritrophin found in the mite gut and faecal pellets within the upper epidermis [89] and a chitinase-like protein [135] found in the mouthparts, legs and exoskeleton of mites. A protein with sequence similarity to DNA translocase FTSK, which from immunostaining was located around the mouthparts and the legs, was found to bind antibodies from a scabies infected chamois and a rabbit [136]. These three proteins have not been studied for the prevalence or degree of antigenicity.

Scabies tropomyosin has been defined and studied showing little IgE antibody binding [107] as also found for house dust mite tropomyosin [2]. The house dust mite study did show variable IgG binding to tropomyosin for scabies patients, but this was not noted by Naz et al. [107]. Recombinant tropomyosin is well structured [137] and has been produced as a highly antigenic recombinant protein for many species [108] so its lack of antigenicity is noteworthy considering, by analogy with the house dust mite [113], it is probably an abundant protein.

The usefulness of recombinant allergens depends on the authenticity of their structure. Natural type II/I apolipophorin-like proteins not only exist bound to lipid in nature but are unstable [129]. Studies to date with peptide fragments of this protein have shown high antigenicity but there is a need to make a systematic study to ascertain the best peptides for use. A recombinant homologue has been successfully produced in insect cells and used to study bee venom allergy [128]. Both isolated and natural paramyosin are unstable but the full-length house dust mite paramyosin has been produced in high yield in *Escherichia coli* [130], but as done for *Schistosomiasis japonica* [138], it would need to be purified from degradation products. The house dust mite arginine kinase has been produced in *E. coli* as a soluble protein in high yield with high antigenicity and enzymatic activity [114]. Cysteine

Table 4.1 Defined scabies antigens

Antigen	Function location	Antigenicity	Recombinant	Immunologically relevant homologues
II/I apolipophorin/ vitellogenin [56, 105, 123, 125]	Large lipid transport and storage protein found in body and eggs	High IgG and IgE binding protein with demonstrated T-cell stimulation	Only fragments tested. Insect expression feasible (Blank)	Allergen in bee venom [128] and house dust mites [129]
Paramyosin [107, 124]	Muscle contraction	IgE in 80% of crusted scabies and IgG binding in 40%	Fragment examined but can be produced in *E. coli* (Banerjee and purified (Jiz))	Minor group 11 house dust mite allergen [130]; vaccine candidate against red spider mite [131] and helminths [132]
Arginine kinase [2]	Mainly muscle, energy transfer	House mite homologue binds IgG and IgE of scabies infected subjects	Enzymatically active *D. pteronyssinus* homologue produced in *E. coli*	87% sequence identity to group 20 house dust mite allergens [114, 115]
Glutathione-*S*-transferase [104]	Large multi-functional family	IgE binding in crusted scabies but possible IgG cross-reactivity with helminths	High yield of glutathione-binding protein produced in *E. coli*	Major cockroach allergen [133] and minor cross-reactive house dust mite [134]. Possible cross-reactivity with helminth antigen [104]
MADF [125]	Unknown function found in mites, burrow walls and eggs	25% of dogs have IgG binding	High yield of full-length protein from *E. coli*	
Cysteine protease [56]	Gut and burrow	IgE, IgG4 and T-cell responses	Expressed in *E. coli* as non-functional protein and no structural documentation	Low sequence identity to group 1 house mite allergens
Inactive cysteine protease paralogue [56]	Gut and faeces [121]	IgE, IgG4 and T-cell responses	Expressed in *E. coli* with undocumented function or structure	
Serine protease [56]	Probably in gut and faeces with inactive paralogues	IgG4 and T-cell responses	Expressed in *E. coli* with undocumented function or structure	46% sequence identity to house dust mite allergens and 40% to mosquito
Ferritin [127]	Not documented	IgG and IgM binding	Expressed in *E. coli* with undocumented function or structure	High, 75%, sequence identity with weak house dust allergen (group 30) and 55% with tick ferritin.

proteases have proved to be difficult to produce as recombinant proteins but this has been accomplished for house dust mite using the pro-enzyme sequence in yeast [139]. Similarly serine proteases are not readily expressed on *E. coli* but can be in yeast [140]. Well folded self-assembling ferritin has been readily produced in *E. coli* [141] and recombinant house dust mite ferritin is very antigenic [142].

4.11 Vaccination

A case has been made for scabies vaccination especially for preventing the sequelae of kidney disease and rheumatic fever caused the coinfection of scabies lesions with group A streptococci [143]. It is also an economically important disease for pig and rabbit farming and companion animals and also infects many species of native wildlife including wombats in Australia, bears in North America and ibex in Spain.

The possibility of vaccination was first documented when the vaccination of rabbits with house dust mite extract was found to confer a degree of resistance to infestation by *Sarcoptes scabiei* var. *canis* [144]. About 75% were completely immune and those infected had lower parasite loads. Resistant hosts developed lower antibody titres to the scabies infection and produced antibodies to fewer scabies antigens. Their transient lesions were composed of neutrophils, plasma cells, macrophages and mononuclear cells but plasma cells were diminished compared to non-resistant hosts. This suggested the possibility of increased Th1 immunity with down-regulated Th2 and antibody responses. This gives some proof of principle but the rabbit model was unusual in producing lesions with intense plasma cell infiltration [145]. A similar study in which chromatographic fractions of goat scabies extracts were used to immunise goats against goat scabies failed to produce protection [146].

Several recombinant antigens have been tested for vaccine potential. Harumal et al. [123] used rabbits infected with dog scabies to test recombinant antigen fragments of the apolipophorin and found no protection although the fragments would not represent the complete potential of this protein. A further trial of two recombinant antigens designated Sslambda15 and Sslambda20B3 in rabbits infected with rabbit scabies found no protection [147] but vaccination with a cocktail of two recombinant chitinase-like proteins has shown protection for rabbits [148]. These antigens that in nature are located in the mouthparts and on the exoskeleton of mites [135] completely protected 74% of the rabbits from developing detectable lesions. A second trial completely protected 85% of rabbits. The lesions that did develop had less hyperplasia and thickening of the epidermis less cellular infiltration with less aggregation of eosinophils [148].

4.12 Conclusions

As reported to date the cellular infiltrate in scabies lesions of humans typically appears to be dominated by Th2-type $CD4^+$ T cells and to contain type 2 macrophages that produce the powerful itch mediator IL-31. Studies with peripheral blood

however suggest that Th1-type memory cells that respond to scabies antigens can be found in subjects with ordinary scabies while the memory responses for subjects with crusted scabies show a more Th2-phenotype. Both of these conclusions however are based on single studies and there is clear variation in that both ordinary and crusted scabies lesions contain $CD8^+$ cells. The Th2 nature of the response of subjects with scabies is consistent with the high levels of IgE antibody to scabies antigens and the hyper IgE immunoglobulinemia in crusted scabies patients. Since crusted scabies patients have levels of IgE antibodies in the range commonly found for atopic dermatitis, it is possible that all of the increased IgE immunoglobulin in their sera is comprised of antibodies. IgG antibodies are also found, and these persist longer than the IgE which has been reported to decline with the removal of the parasites, a finding reminiscent of the IgE response to the epicutaneous application of contact sensitisation agents. The finding that pigs show Th17 type responses in crusted scabies lesions raises the possibility that they might be involved in human disease, but they have not been reported and indeed IL-17 was noted for its absence in ordinary scabies lesions. Sequential waves of Th1, Th2 and Th17 responses have however been described in immune responses to chronic epicutaneous exposure to contact sensitising antigens so this might be expected to occur in persistent scabies or scabies induced by the high-dose inoculations used by experimenters. A worthwhile consideration is that the type of responses found in persisting scabies lesions might not be the type of responses that provide resistance to infection and these have not been examined. Resolving scabies lesions have been reported to be dominated by an inflammatory dendritic cell infiltration, distinct from Langerhans cells, that suggests an inflammatory T-cell response.

The cross-reactivity of IgE antibodies with proteins induced by the house dust mite has been noted for years and compromises the use of house dust mite extracts for allergy diagnosis and epidemiological studies. Importantly however, the cross-reactive proteins are not the immunodominant allergens of house dust mites, so scabies infection can be easily distinguished with the use of purified allergens, now being performed with microarrays for experimental purposes. There is also no reason to suspect that the profile of house dust mite allergens and scabies antigens will be similar although the genomic sequences now available would make investigation with recombinant components possible, noting that they need to be produced with authentic structure. The very high binding of IgE antibodies to the minor house dust mite allergen arginine kinase (Der p 20) not only illustrates this point but provides a useful reagent for serological diagnosis of scabies as does the type II/I apolipophorin protein of scabies that, at least in peptide constructs, has minor cross-reactivity with its Der p 14 equivalent.

An important advance has been introduction of recombinant antigens and now genome sequences for comprehensive antigen analyses. Follow up with production of recombinant antigens with authentic structures will be needed and perhaps some impetus for this would be the need to distinguish scabies infection from house dust mite allergy. Peptides representing T-cell epitopes of scabies antigens could have more immediate application especially used in conjunction with new gene expression technologies for measuring cellular responses. The antigen analysis has

however led to identification of chitin-binding-like proteins that show vaccination potential in rabbits, and this is being actively investigated.

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Biochemical Research of *Sarcoptes scabiei*

5

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5.1 The Need for Biochemical Research

Biochemical research of the *S. scabiei* plays a major role in understanding this parasite's biology and adaptations for its survival in its mammalian hosts, which will help in the development of new control and diagnostic strategies. *S. scabiei* infects almost all mammals. Currently, the scabies mite is classified taxonomically as a single species with different varieties based on host specificity [1] and its zoonotic potential is limited but possibly not completely negligible [2, 3]. Mechanism underlining the host specificity of *S. scabiei* variants is yet to be discovered to address which mite variants are infective for which hosts and which hosts are resistant to which mite variants.

S. scabiei var. *hominis* alone accounts for 200–300 million human infestations annually of which a minor fraction develops into the life threatening complicated stage of the infestation, crusted scabies [4]. Scabies infestation is very often associated with secondary bacterial infections, mainly of *Staphylococcus aureus* and *Streptococcus pyogenes*. In these cases, the primary uncomplicated parasitic

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infection turns into a much more complicated state with pyoderma, post-streptococcal glomerular nephritis, rheumatic fever and rheumatic heart disease [5–10]. Secondary infections with pathogenic bacteria are biochemically supported by the excretion and secretions of the mite [11–13] and the altered microenvironment may possess favourable conditions for the mite as well as the bacteria. Detection of the scabies mite in the clinical setting largely relies on microscopic observation of skin scrapings or in some instances on direct dermoscopic observations. Both diagnostic methods have low sensitivity and require microscopy skills. Biochemical research is needed to develop an easy, rapid and, highly specific and sensitive diagnostic test to detect the presence of scabies mites. Another challenge in controlling this parasite is the development of resistance against commonly used scabicides, topical permethrin and oral ivermectin [14–16]. Their widespread use and an often observed patient incompliance to treatment regimens are likely leading to the increased appearance of drug resistant parasites; hence, finding new drug targets and developing new treatments are crucial in controlling this disease in the future. To face the above challenges we need a better knowledge of the molecular biology and biochemistry of this parasite. Current knowledge about proteins that are involved in biochemical processes has given a first insight into host–parasite interactions to a certain level (summarised in Table 5.1); yet, more research is needed to accomplish the ultimate goal to develop effective diagnostics and therapeutics.

Table 5.1 Summary of scabies mite proteins that have been functionally characterised

Protein group/family	Protein name and accession number	Significance	Function(s)	Localisation within the parasite	Ref.
Chitinase-like proteins	Chitinase-like protein 5 (*Ss*CLP5), *KPM08736*	Immunogenic protein and potential serodiagnostic markers and vaccine targets	Constituent in exoskeleton providing protection	Exoskeleton	[56]
	Chitinase-like protein 12 (*Ss*CLP12), *KY904739*			Exoskeleton	[75]
Tropomyosin	Tropomyosin (*Ss*Tm) *JF922117*	Immunogenic protein and potential vaccine target	Muscle contraction	Musculature	[58]
Calmodulin	Calmodulin (CaM) *KX347068*	Immunogenic protein and potential serodiagnostic marker	Ca^{2+} ion binder facilitating cell signalling, inflammation, energy metabolism, apoptosis, immune response and muscle contraction	Haemolymph	[55]
Thioredoxin peroxidases	Thioredoxin peroxidase *KC693033*	Immunogenic protein and potential serodiagnostic marker	Antioxidant protecting the mite from reactive oxygen and from host-activated leukocytes	Integument musculature	[76]
Inorganic pyrophosphatase	Sar s 32 allergen inorganic pyrophosphatase-like protein (PYP1) *KPM05552*	Potential serodiagnostic marker	Involved in energy- and lipid metabolism, and in nucleic acid and protein synthesis	Integument faeces	[25]
Serine protease	Sar s 3 Yv7016G03 *AAR14081*	Potential therapeutic target	Digestive protease, cleaves human filaggrin and potentially other host proteins	Digestive system Faeces	[28]

(continued)

Table 5.1 (continued)

Protein group/family	Protein name and accession number	Significance	Function(s)	Localisation within the parasite	Ref.
Scabies mite inactivated serine protease paralogues—SMIPP-Ss	Group 3 allergen SMIPP-S Yv6023A04 (SMIPP-Ss I1) *AAR14091*	Immune-modulatory protein. Potential therapeutic target	Host immune evasion by inhibiting the host complement system	Digestive system Faeces	[30, 32, 34]
	Group 3 allergen SMIPP-S YvT004A06 (SMIPPS-D1) *AAR14095*				
Peritrophin	Peritrophin (PTP) *JF266566*	Potential drug target	Potentially involved in digestion and protection against mechanical, chemical damage and infection	Digestive system Faeces	[33]
Serine protease inhibitor	Serpin (SMSB3) Yv7088B02.2 *JF317220*	Immune-modulatory protein. Potential therapeutic target	Host serine protease inhibition. Host immune evasion by inhibiting the host complement system	Digestive system Faeces	[35]
	Serpin (SMSB3) Yv5004A04.2 *JF317222*				
Scabies mite inactivated cysteine protease paralogues—SMIPP-Cs	Sar s 1 allergen SMIPP-Ca Yv4025A02 *AAS93672*	Therapeutic target. Causes pathological skin microthrombi formation	Host immune evasion by procoagulation and delay in fibrinolysis	Digestive system Faeces	[31, 37]
	Sar s 1 allergen SMIPP-Cc Yv5009F04 *AAS93675*				
	Sar s 1 allergen SMIPP-C Yv4028C12 *AAS93674*		Potentially host immune evasion		
Glutathione S transferases (GST)	Glutathione S transferase SAS0751 *BM522085*	Drug and vaccine target	Detoxification and a potential contributor to drug resistance	Integument haemolymph	[77]
Enolase	Enolase-like protein *KPM02829*	Potential serodiagnostic marker and vaccine target	Involved in glycolytic and gluconeogenesis pathways and host immune evasion	Integument digestive system Reproductive organs	[63, 78]

5.2 Parasite Biology and Host–Parasite Interplay

5.2.1 Biochemical Discoveries on Scabies Mite Biology

Recent proteomic analysis of *S. scabiei* var. *canis* mite and egg aqueous extracts and insoluble fractions gave initial insights into biological processes in the mite. Membrane biology such as cell adhesion, cell migration and proliferation in the scabies mite could be mainly regulated by tetraspanins, as there are ten tetraspanin-like proteins and eight others with the tetraspanin domains in the mite proteome [17]. The tetraspanins of *Drosophila* have a wide range membrane functions, including cell junction formation, synapse formation, notch dependent developmental processes and light dependent retinal degeneration [18]. Knowledge on crucial biological processes, such as oxygen uptake mechanisms and respiratory system development in the scabies mite are lacking. However, the homologs of *trachealess (trh)* and *Scribble* genes, which are responsible for tubulogenesis including trachea and salivary glands of *Drosophila,* have been found in *S. scabiei* var. *suis* transcriptome [19–21]. Another tubulogenesis gene required for the tracheal branch migration in embryonic tracheal development, *breathless (btl)* was not found in the current *S. scabiei* databases; however, growth factor genes *sevenless* and EFGR which can be substitutions for the *btl* were present in *S. scabiei* transcriptome [20, 21]. Therefore, the *S. scabiei* may also have a branched tracheal system which should be explored further by mite histology. Even though the *S. scabiei* respiratory system is unexplored, the presence of the oxygen transporting and utilising proteins such as oxygen and haem-binding proteins, globin proteins, cytoglobin like protein and neuroglobin like protein [19] indicates the importance of oxygen in mite biology and in metabolism.

The scabies mite metamorphism is likely to be regulated by ecdysteroids, as described in other insects [22]. *S. scabiei* mites are highly susceptible to dehydration, and their cuticle plays a major role in water homeostasis. This was further highlighted by the discovery of 24 different proteins in its proteome that are potential constituents of the cuticle [19, 21]. Chitin is the major component of the cuticle, and along with chitinases, which hydrolyse the chitin (Table 5.1), and the chitin synthase, which promotes the chitin polymerisation, are the most important proteins involved in metamorphism and responsible for reabsorption of the old cuticle and development and hardening of the new cuticle.

Mass spectrometry analysis of *S. scabiei* whole body extracts revealed that its locomotor system mainly consists of actin, myosin and tropomyosin [17] (Table 5.1). Calmodulin and calsequestrin-2-like proteins, which are thought essential for the muscle functions (Table 5.1), are also present in the *S. scabiei* proteome. Homologous proteins present in haematophagous arthropods, such as ferritins, cathepsins, glutathione-S-transferases and thioredoxins, are also found in the scabies mite (Table 5.1). Glutathione may function in detoxification; however, approximately 40% gene silencing of glutathione-S-transferases mu1 did not show any visible impact on mite survival [23]. Thioredoxin peroxidase (*Ss*TPx), found in muscles, integument and anterior and posterior ends of the mite, potentially acts as an

antioxidant protecting the mite from reactive oxygen species and host activated leukocytes [24] (Table 5.1).

The *S. scabiei* digestive processes are not completely described yet, even though several studies have been carried out to investigate individual digestive enzymes. An inorganic pyrophosphatase found in mite cuticle, tegument and the faecal pellets may have functions in the lipid metabolism and regulation in nucleic acid and protein synthesis [25] (Table 5.1). *S. scabiei* has one active serine protease (Sar s 3) expressed in the mite digestive system and excreted in to the host epidermal burrow with the mite faeces (Table 5.1). Sar s 3 is thought to be a digestive enzyme with the ability to digest human skin filaggrin, which is a key component of the epidermal cornified cell envelope [26]. In addition, a *S. scabiei* aspartic protease has been shown to digest [27] human fibrinogen, fibronectin, serum albumin and haemoglobin, all of which are possible nutritive materials that mites ingest while living in the skin.

5.2.2 Scabies Mite Host Immune Evasion

As the scabies mite is an obligatory burrowing parasite, the host immune system is a major threat to its survival and propagation. Therefore, parasitic adaptations are expected to have evolved in *S. scabiei*. One major adaptation was found to be the expansion of protease classes with immune evasion functions. While free-living, non-parasitic mites principally have one group 1 and one group 3 allergen, which are proteolytically active proteases, the parasitic scabies mite exhibits a completely different repertoire. In the scabies mite, the group 1 and 3 allergen classes are amplified to 34 and 10 members, respectively. Apart from the proteolytically active Sar s 3 [28], 33 inactivated serine protease paralogues (SMIPP-Ss) have been identified [29]. In addition, there are five proteolytically active homologs to the group 1 allergens and 5 scabies mite inactivated cysteine protease paralogues (SMIPP-Cs) [29]. Their localisation inside the mite gut and within the mite faeces excreted into the host skin suggests that they may have roles within the mite intestinal system and within the environment of the mite [30, 31]. Among the 33 SMIPP-Ss at least five (SMIPP-S G2, G4, D1, B2, I1) are complement inhibitors [11, 29, 32] (Table 5.1). Mite excretory and secretory proteins released by the mites while burrowing through the skin are thought to activate the host complement system. Complement components are ingested by the mites and have been co-localised in the mite gut with the SMIPP-S proteins [32]. In addition, peritrophin, which is a triggering molecule for the lectin pathway, has been found in mite gut and in the faecal pellets [33] (Table 5.1). This finding further consolidates the hypothesis of host complement cascade activation in the mite gut undoubtedly a major threat to the mite survival. Nevertheless the mite manages to overcome the onslaught of host defence, presumably by inactivating the complement pathway with SMIPP-S proteins. SMIPP-S D1 and I1 have been shown to bind to the complement components; C1q, mannose binding lectin (MBL) and properdin, and thereby interfere with all three pathways of complement activation [32]. SMIPP-S protein binding to C1q displaces or

inhibits the C1r/C1s enzymes and/or causes conformational changes to the C1 complex, which inhibits the activation of the classical pathway. The main SMIPP-S target of the lectin pathway is Mannose Binding Lectin (MBL). The binding of SMIPP-Ss to MBL causes conformational change in the MBL complex, which inhibits the Mannose associated serine proteases (MASPs) and also releases them from the MBL complex, thereby interfering with the downstream pathway activation [34]. Properdin positively regulates the alternative pathway by binding to C3b, thereby stabilising the C3 convertase for prolonged half-life and inhibiting the proteolytic activity of factor 1. SMIPP-Ss binding to properdin prevent the assembly of alternative pathway convertases, thereby interfering with the alternative pathway [32]. In addition to these pseudo-proteases, the host innate immunity is also suppressed by a group of scabies mite serine protease inhibitors/serpins (SMS) [35] (Table 5.1). SMSs B3 and B4 were localised in the mite gut and mite faeces. These Serpins did not inhibit mite serine or cysteine proteases but the mammalian chymotrypsin like serine proteases [35]. In addition to their protease inhibitory activity, SMSs inhibit the all three pathways of complement activation [35]. SMSB4 binds to the complement components: C1, properdin, MBL, C4, C3, C6 and C8, while SMSB3 binds to C4, C3 and C8. In contrast to the SMIPP-Ss, there was no complex formation by SMS with the C1r, C1s and MASPs [35]. With no doubt, mites have successfully adapted to evade the first-line host defence, the complement system.

In addition to the host immune evasion, SMIPP-Ss and SMS have been found to facilitate the propagation of scabies associated bacterial species, *S. pyogenes* and *S. aureus*, which could be interpreted as synergistic behaviour of mites and pathogenic bacteria. The host innate immune system defends against the pathogenic bacteria by releasing chemo-attractants (C3a and C5a) to activate inflammatory cells, Cb3 deposition on the pathogens for the activation of phagocytosis and by incorporation of membrane attack complex (MAC) into the pathogen surface, leading to lysis. If the complement system activation pathways are blocked by excreted mite complement inhibitors (as described above), the resultant complement inhibition affects the growth of bacteria. This has been demonstrated *in vitro* for group A streptococcus (GAS) [11] and *S. aureus* [12].

The second group of inactive proteases also seems to be involved in host immune evasion. Scabies mite inactivated cysteine protease paralogues (SMIPP-Cs) [36] are expressed in the mite gut, highly in female mites compared to other life stages, and also excreted with mite faeces into the burrows [31]. SMIPP-Cs form multicopy family of 5 members homologous to house dust mite (HDM) group 1 allergens. All SMIPP-Cs have mutated catalytic sites. Two of them, SMIPP-Ca and SMIPP-Cc have been shown to accelerate fibrin formation and were localised in dermal microthrombi in human scabies patient histology [37] (Table 5.1). Furthermore, SMIPP-Cs alter the polymerised fibrin structure and delay the plasmin induced fibrinolysis. In relation to above findings, detection of microthrombi with the absence of vasculitis is a common pathological observation in scabetic skin (personal communication with Dr. Bernard Cribier, Universitaires et Université de Strasbourg, France and Dr. Nicolas Ortonne, Henri Mondor Hospital, France) and have been documented [38].

Possibly, the SMIPP-C induced microthrombi trap host immune cells, antibodies and complement components, thereby preventing exposure of the mite to host defence mechanisms.

5.3 Biochemical Interactions Between the Mite and the Host

Parasite excretory and secretory proteins are mainly responsible for the host–parasite interactions. Penetration of the mite into the host skin involves dissolving the stratum corneum with secretory molecules and mechanical burrowing using the legs or chelicerae [39]. Salivary glands could be responsible for the excretion of these molecules. Hundreds of salivary gland proteins were discovered in *S. scabiei* predicted proteome [40], yet the functional properties of these need to be explored. Knowledge about the immunogenicity of the mite proteins in the host tissues is not only important to understand the host–parasite interactions but also for the identification of vaccine and diagnostic targets. Among 95 proteins analysed from the *S. scabiei* var. *canis* mite extracts, 62 proteins were recognised by the host immunoglobulins; IgM or IgG or by both [41], demonstrating parasite antigen recognition by the host and a possible avenue for vaccine development. The remaining proteins that were not recognised by the host immunoglobulins are equally interesting candidates for therapeutic applications, due to their possible function in host immune evasion and/or host immune modulation. Antibody expression profiles in common versus crusted scabies patients are vastly different, due to the different mite proteins being recognised by the host immune system in each disease manifestation. Six identified Glutathione S transferases in *S. scabiei* (*Ss*GST) are related to the mu, delta and epsilon classes of GST and are allergens (Table 5.1). The Mu class is related to mammals whereas delta and epsilon classes are related to insect GSTs. Antibodies against *Ss*GST were found in both crusted and common scabies patients [42]. The invertebrate protein paramyosin, a major allergen in HDMs, is also present in *S. scabiei* (Sar s 11). Immunoglobulins against paramyosin were primarily recognised by individuals infested with common scabies [43]. *S. scabiei* apolipoprotein (Sar s 14.3), expressed in the cuticle and the internal organs of the mites and eggs, is also recognised by the immune system of the host, and significantly greater immunoglobulin expression was seen in the crusted scabies [44]. However, Sar s 14.3 only exerted transient protection, as the levels of immunoglobulins declined in the mid to late stage of the infestation and failed to provide protective immunity to the rabbits vaccinated with Sar s 14.3 [45, 46]. In both, common and crusted scabies, the *S. scabiei* cysteine protease Sar s 1d elicited a strong immune response with elevated peripheral blood mononuclear cells (PBMCs), and the elevations in IL5, IL13 and IFN-γ were significantly higher in crusted scabies [44]. Scabies mite apolipoprotein, Sar s 1d and SMIPP-Cc elicited significantly higher IgE response in the crusted scabies than in the ordinary scabies, while the apolipoprotein gave the highest and Sar s 3 showed no difference in IgE response [44].

5.4 Applications of Biochemistry in Developing Advanced Diagnostics and Therapeutics for Scabies

5.4.1 Discoveries of Potential Diagnostic Markers

Serum antibody detection in the *S. scabiei*-infected animals and humans has been assessed as a promising diagnostic method in several studies. However, achieving scabies specificity will be challenging because many *S. scabiei* proteins have homologous counterparts in the house dust mites. House dust mites are ubiquitous and a large portion of scabies patients will have antibodies against HDM proteins. Chitinase, which cleaves the chitin in the exoskeleton, also contributes to inflammatory reactions during infections [47]. Scabies mite chitinases belong to a multicopy gene family [21] and *S. scabiei* chitinase-like protein secretion was upregulated upon host infection [48]. *S. scabiei* chitinase-like protein and tyrosine have shown promising early detection of antibodies in infested rabbits (96.7%–100% detection within the first week of infestation, with 94.4%–95.2% sensitivity and 86.7%–94% specificity [48, 49]). Furthermore, a chitinase-like protein has been localised not only on the surface of the mite but also in the host tissues [48] which gives additional value to the accuracy for the diagnostic tool (Table 5.1). Similarly, *S. scabiei* recombinant inorganic pyrophosphatase (Ssc-PYP-1) elicited high antibody titres at week 1 of the infestation in rabbits with a sensitivity of 92% and specificity of 93.6%, providing early detection of the infestation [25]. Even though the knowledge on PYP in arthropods is limited, it is involved in energy metabolism, development and moulting in other parasites [50, 51]; therefore, it appears to be a promising vaccine and therapeutic candidate. Cofilin protein modulates the actin dynamics, including cell migration, morphogenesis, endocytosis and cytokinesis in nearly all eukaryotic cells. *S. scabiei* cofilin was found only in the splanchnic area of the mite and has shown 83.33% sensitivity and 87.9% specificity towards the serum containing antibodies against cofilin in rabbits [52] (Table 5.1). The concentration of acute phase proteins (APPs) in circulation changes in the event of infection, inflammation trauma or stress and this provides information on disease severity and the extent of tissue damage. Hence, the APPs can be used as diagnostic targets. *S. scabiei* amyloid A, haptoglobin, α1-acid glycoprotein and ceruloplasmin were identified as APPs in *Capra ibex* [53] and have been proposed to be used to diagnose scabies in free ranging animals. However, Morgan et al. (2017) pointed out that only 33 out of 54 tested proteins (66%) have been recognised by the infected human serum, and only 14 of the selected potential diagnostic candidates had only about 67% sensitivity and 40% specificity [54]. In addition, *S. scabiei* calmodulin protein (CaM) with typical calcium binding properties, was widely spread in the mite haemolymph and was absent in the host epidermis (Table 5.1). It has been assessed as a potential serodiagnostic marker with little success. Serodiagnotics of CaM in naturally infested rabbits revealed low specificity (22.5%) of detecting *S. scabiei* infestation [55]. *S. scabiei* thioredoxin peroxidase (SsTPx) with essential antioxidant

functions, found in mite muscle tissue, and integument has detected with 95.3% sensitivity and 93.8% specificity in infected rabbits by using a dot-ELISA method [24]. However, its high homology to *Psoroptes cuniculi* TPx with 98.77% identity resulted in antibody cross-reactivity and only 68.3% specificity [24], which reduces its potential value as a serodiagnostic marker.

5.4.2 Promising Therapeutic and Vaccine Targets

To date there is no vaccine against scabies. Current chemotherapeutic agents for scabies treatment are suboptimal, and drug resistance is an emerging concern. Therefore, novel therapeutic or vaccine targets should be explored. Several vaccine candidates have been proposed with some promising results. *E. coli* expressed *S. scabiei* chitinase-like protein 5 (r*Ss*CLP5), an exoskeleton protein, has been used to immunise rabbits [56] and high immunogenicity with raised IgG at 1 week post-immunisation was reported, which remained high for about 3 months. The immunisation resulted in 74.3% of rabbits protected against the challenge dose of mites with no detectable clinical signs and a low mite burden, compared to the control group [56]. The rabbits were immunised with 2 injections of recombinant proteins with 15 days interval as subcutaneous injections. A cocktail vaccine, including two recombinant components, r*Ss*CLP5 and r*Ss*CLP12 showed the highest protection (85%) against a mite challenge of 2000 mites, compared to vaccination with the individual r*Ss*CLP5 (75%) or r*Ss*CLP12 (70%) [57]. Several other immunogenic proteins (Ssag1 and Ssag2 [46, 58, 59] and Ssλ20 [60]) with demonstrated ability to elevate serum IgG levels have been tested for potential vaccine use, but with little success.

Almost all the therapeutics currently used against *S. scabiei* have been developed to treat different parasitic diseases, yet they are found to be effective against scabies and mange. The most commonly used topical scabicide, 5% permethrin acts on the arthropod nervous system, as it prolongs the opening of the voltage sensitive sodium channels (VSSCs) thereby causing paralysis and death [61]. The second most used drug to treat scabies is ivermectin, which causes irreversible opening of ligand gated ion channels in invertebrates, leading to hyperpolarisation followed by paralysis and death. In *S. scabiei,* ivermectin activates the chloride channels (*Ss*Cl) irreversibly in pH dependent manner [62]. Several novel candidates in addition to drugs already in use against other parasites are currently under investigation for scabies treatment.

A novel compound, octadecanoic acid-3, 4-tetrahydrofuran diester obtained from neem oil, has been tested for its novel acaricidal activity on *S. scabiei* var. *cuniculi* mites [63, 64]. Through transcriptomics, 45 differentially expressed genes in the tricarboxylic acid cycle paths and 60 differentially expressed genes in the oxidative phosphorylation pathway, including cytochrome C oxidase cbb3 subunit, cytochrome C reductase b/c1 subunit, ATP synthase and NADH dehydrogenase were observed to be downregulated after treatment. In addition, enolase (a glycolytic protein that is thought to reduce host immunity against parasitic immune

evasion) and superoxide dismutase (which protects mites from oxygen-free radicals) were downregulated in the mite transcriptome upon treatment with octadecanoic acid-3, 4-tetrahydrofuran diester [63]. According to these data octadecanoic acid-3, 4-tetrahydrofuran diester interferes with the mite energy metabolism. In addition, it downregulates the protein vitellogenin, a key protein in arthropod vitellogenesis, thereby potentially inhibiting the development of mite ovaries [63]. A monoterpene,1,8-Cineole (also called eucalyptol) which has been found in many essential oils with antimicrobial, antifungal, anti-inflammatory, antioxidant and anticancer properties, is also effective against *S. scabiei* var. *cuniculi* with an LC_{50} of 2.77 mg/mL in 24 h and LT_{50} of 3.6 h at the concentration of 9.2 mg/mL [65]. Post-1,8-Cineole-treatment enzyme activities of superoxide dismutase (SOD), GST and monoamine oxidase (MAO) were increased, while acetylcholinesterase (AChE) activity was supressed [65]. SOD and GST associate with the parasite protection mechanisms; therefore, their upregulation indicates the mites' response to the lethal effects of 1,8-Cineole. At high concentrations of 1,8-Cineole, nitric oxide synthase (NOS) activity was supressed while at medium and low concentrations, its activity was increased. Due to its effect on the nervous system components; AChE, NOS and MAO, 1,8-Cineole was predicted to act on mite nervous system [65]. Lemongrass oil (citral), manuka oil (beta-triketones), tea tree oil (terpenoids), clove oil, palmarosa oil and eucalyptus oils were found to be effective against *S. scabiei* motile mites [66–68]. The functional targets of the active compounds within the above mentioned oils are yet to be determined. However, it is interesting that the manuka oil and lemongrass oil [66] seem to be highly effective against immotile scabies eggs, when almost all other available drugs fail to kill this amplification stage of the *S. scabiei* life cycle [69].

5.4.3 Emerging *S. scabiei* Scabicide Resistance

Due to patients' incompliance to repeat treatment regimens and repeated use of the same drug over long periods of time and against a range of infectious diseases, scabies mites are on the verge to develop resistance to commonly used treatments. In *S. scabiei* parasites, permethrin resistance has emerged with a single nucleotide polymorphism in the VSSC gene [70]. In addition, increased transcription of the GST gene has been observed in the permethrin resistant mites. GST is known to metabolise permethrin; therefore, increased transcription of GST in resistant mites indicates GST-mediated acaricidal resistance in *S. scabiei* [71]. Mites have also developed resistance to the most used systemic drug used against scabies, oral ivermectin [14, 72]. The proposed mechanisms of *S. scabiei* resistance to ivermectin is through ABC transporters, such as commonly known multidrug-resistant P-glycoprotein [73, 74]. Nine types of ABC transporters have been identified in the S. scabiei EST database, including the ABC-B (P-glycoprotein) and ABC-C groups, which are implicated in drug resistance in *Drosophila* and *Anopheles,* due to their broad and sometimes overlapping substrate specificity [73].

5.5 Conclusion

Biochemical research of scabies parasites has certainly helped to advance the research field of scabies. Yet, extensive investigations of the molecules that are being discovered in the emerging genomic and proteomic databases are required, to understand the scabies mite biology in depth. This will facilitate the discovery of novel diagnostic, therapeutic and vaccine targets that are very much in need to develop novel control strategies against scabies.

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Scabies Multi-Omics to Identify Novel Diagnostic or Therapeutic Targets

6

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6.1 Introduction

Compared to many other parasites, *Sarcoptes scabiei* is poorly understood at the molecular level. Analysing the molecular make-up of this parasite will inform our understanding of its biology. Here we discuss the implications of a multi-omics approach for detailed investigations of molecular mechanisms and pathways associated with parasitism, egg and larval development and pathogenicity, which may lead to the identification of novel intervention targets and ultimately to the development of diagnostics and drugs.

6.2 Potential of Multi-Omics Strategies

Omics technologies, such as high-throughput sequencing, transcriptomics and mass spectrometry-based proteomics, are now frequently being used by biological researchers. Multi-omics uses a number of distinct omics technologies and focuses on integrating data sets, analyses and/or experimental results to achieve a deep understanding of molecular mechanisms, processes or pathways.

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The datasets mainly used are the genome (complete set of DNA of an organism including genes, non-coding DNA, mitochondrial DNA), the proteome (entire set of proteins expressed at a certain time), the transcriptome (all RNA molecules including mRNA, rRNA, tRNA and other non-coding RNAs), the metabolome (complete set of small-molecule chemicals found within a biological sample) and the microbiome (the genetic material of all microorganisms in a particular environment, e.g., an organism). If biological material is assumed or known to originate from multiple organisms and, therefore, contains multiple 'omes', the inclusion of the prefix 'meta' is usually included. For an acarid organism, a metagenome would be the combined genomes of the mite and all microbes contained inside it and on its surface. 'Omes' are related to each other in a hierarchical fashion, e.g., the genome contains the ORFeome (complete set of protein-coding sequences), which gives rise to the transcriptome, which is translated to the proteome. The more information can be gained from the integration of multiple 'omics' data sets, the more complex the analyses and, hopefully, the better the insights into an organism's biology. For example, while transcriptomics can inform which genes are transcribed when and where in the organism, proteomics is a technology to identify and quantify proteins, their modifications, excretion/secretion and interaction(s). If we take this even further and explore an entire microenvironment, such as a scabies mite-infested skin sample, an integrated multi-omics approach has, in theory, the potential to explore the molecular, physiological and biochemical processes and pathways in this entire ecosystem (represented by mite, bacteria and host), thereby offering insight into the pathogenesis of scabies disease. Furthermore, multi-omics may be useful in translational applications. Anti-parasitic drugs usually interfere with processes that are essential for parasite survival, but the targets of many therapeutics or therapeutic candidate drugs are not known and mechanisms of action not understood. Multi-omics approaches may offer avenues to understand how the parasite responds to external challenges, for example, how drugs interfere with underlying pathways in the mite.

Is multi-omics an expensive fishing expedition, driven mainly by progress in technology and often lacking a clear understanding of the data? A major challenge seems to be for the traditional biologist to thoroughly mine the data in a multidisciplinary context, involving experts in bioinformatics, molecular biology and statistical expertise, as well as to underpin any conclusions with iterative rounds of testing, complementary experimental data and clinical validation.

6.3 What Work Has Been Done on Mites, and Where Do We Stand in the Scabies Field?

We have summarised the omics technologies recently applied to mites in Table 6.1.

Table 6.1 Applications of omics technologies in study of mites

	Species	Omics approaches	Primary aim of study	Reference
Free-living mite species	*Tetranychus urticae*	Genome and transcriptome sequencing	Drug resistance genes identification; genome size	[1]
		Microarray	Diapause-related genes expression pattern	[2]
		Transcriptomic and proteomic analysis	Diapause pathway elucidation	[3]
		16S rRNA sequencing	Microbiota	[4]
	Metaseiulus occidentalis	Quantitative PCR	Genome size	[5]
		Transcriptome sequencing	Transcripts annotation	[6]
		16S rRNA sequencing	Microbiota	[4]
	Dust mites	Genome and Transcriptome sequencing; microbiome analysis	Genes and allergens identification; genome size; microbiota	[7–9]
		RNA-seq, proteomic analysis and IgE reactivity mapping	Transcriptomes, proteomes and allergenomes characterization	[10]
		Proteomic analysis	Proteomes and allergenomes identification	[11]
		Metabolomics analysis	Host response	[12]
	Chigger mites	Mitochondria genome sequencing	Gene rearrangement	[13]
		Quantitative PCR and k-mer analysis	Genome size	[14]
		16s rRNA sequencing	Microbiome in life stages and after infection	[15]
		Proteomic analysis of pathogen	Host response	[16]
	Dermanyssus gallinae	16S rRNA sequencing	Microbiota	[17, 18]
		Transcriptome sequencing	Functional annotation	[19]
		Transcriptomic and proteomic analysis	Secretome and transmembranome identification	[20]
		Proteomic analysis	Vaccine target identification and evaluation	[21]
	Liponyssoides sanguineus	Genomic study of pathogen	Pathogen identification	[22]
	Ornithonyssus bacoti	RNA-seq	Functional annotation	[23]
		16S rRNA sequencing	Microbiota	[24]

(continued)

Table 6.1 (continued)

	Species	Omics approaches	Primary aim of study	Reference
Obligatory parasitic mite species	*Sarcoptes scabiei*	Expressed sequence tag analysis	Gene identification	[25]
		Quantitative PCR	Genome size	[26]
		Draft genome assembly	Genes identification; proteomes prediction; genome size	[27]
		Proteomic analysis	Diagnostic and vaccine targets identification	[28]
		Genomic and Proteomic analysis	Mite biological processes elucidation	[29]
		16S rDNA/16S rRNA sequencing	Microbiota	[30, 31]
		Metagenome analysis	Microbiota	[32]
		Transcriptome-microRNA analysis	Host response	[33]
	Demodex mites	18S rDNA sequence analysis	Molecular classification and phylogenesis	[34]
		Mitochondria genomes study	Evolution	[35]
		Proteomic analysis of pathogen	Pathogenicity and host response	[33]
		16S rRNA sequencing	Microbiota	[24, 36]
		Quantitative PCR	Genome size	[26]
	Psoroptes ovis	Microarray	Host response	[37]
		Expressed sequence tag analysis	Functional annotation	[38]
		RNA-seq	Transcripts profiling in different developmental stages	[39]
		Whole-genome sequencing	Genome assembly; genome size	[40]
		Genomic and transcriptomic analysis	Developmental stages-specific allergen gene expression	[41]
		16S rDNA sequencing	Microbiota	[42]
		Quantitative PCR	Genome size	[26]

6.3.1 Free-Living Mite Species

The publication of the genome from the two-spotted spider mite, *Tetranychus urticae* [1] in 2011, marked the advent of mite genomics. *Metaseiulus occidentalis* should also be mentioned, a highly effective free-living predatory mite, feeding on pest mites in agricultural crops around the world. Its transcriptome [6] and mitochondrial genome [43] were sequenced a decade ago. These first mite sequencing projects focussed on just two of an estimated half million mite species, of which many have a significant impact on the health of humans, animals and plants. As *T. urticae* is readily cultured *in vitro*, it has become a model for other mites, like *Caenorhabditis elegans* has for parasitic nematodes [44]. Although *T. urticae* is excellent to assist molecular studies of mites, it cannot be used to explore processes that relate specifically specific to parasitism within mammalian hosts. Thus, enhanced resources and integrative 'omics' approaches are needed for a deep understanding of parasitic mites, such as *S. scabiei* for analyses. In contrast to the extremely large genomes of ticks, mites genomes are substantially smaller [26], with that of *T. urticae* being 90 Mb in size and completely assembled [1]. Double-stranded RNA interference (RNAi) has been established for this mite species [45]; hence, there is promise to develop a similar platform to enable functional genomic investigations of parasitic mites of medical and veterinary importance.

Compared to scabies, house dust mite allergy has been far more studied, partially because research funding to study this disease might have been easier to obtain, but also because house dust mites can be cultured and do not require animal models for study. Already in 1988, the first gene of the house dust mite *Dermatophagoides pteronyssinus* was described. A substantial genome transcriptome and microbiome study of *Dermatophagoides farinae* was published in 2015 [7] representing a vast resource that will, together with more recent databases [24–28, 46, 47], help researchers to understand dust mite biology per se, further our knowledge of mite allergens and may facilitate new avenues to treat house dust mite allergy.

6.3.2 Obligate Parasitic Mite Species

Few parasitic mite species of medical and veterinary importance have been studied using-omics approaches (Table 6.1). Until the early 2000s, almost no experimental and molecular data existed on *Sarcoptes scabiei*, due to the absence of an *in vitro* culture system and an animal model. Since then, a range of molecular databases have been established, including a human scabies mite EST dataset (reviewed in [48]), from which candidate drug and immunodiagnostic targets have been identified, in addition to proteins implicated in allergy, drug resistance and immune evasion. Furthermore, biologically active recombinant molecules representing multiple classes of scabies mite proteins were produced [49–52] and some of their roles in pathogenicity and mite survival were characterised [49, 50, 52–54]. In the absence of an *in vitro* culture for scabies mites, the porcine animal model for scabies provided excellent opportunities for more comprehensive omics studies of this mite.

Advances in high throughput sequencing and informatics have enabled de novo-assemblies and annotation of the scabies mite draft nuclear [46] and mitochondrial [47] genomes, which provided initial resources for multiomic investigations. Future work should focus on enhancing and expanding these resources and then undertaking in-depth explorations of fundamental aspects of mite biology to identify targets for new interventions.

Another focus will be on the exploration of the interplay between the mite and its associated microbiota. Bacteria may be a source of nutrients for the scabies mite [55], they may provide vitamins and minerals, or fix nitrogen. If some bacteria are indeed essential to mite survival, they may be potential targets for therapeutic intervention [55] or the maybe employed as surrogate marker(s) for urgently needed molecular diagnostic tests. Initial studies of the microbiota of *S. scabiei* [30] indicate that it is feasible to elucidate the relationships within the parasite–host–pathogen triangle and to gain an understanding of the clinical correlations between scabies and secondary bacterial infections (Chap. 8).

6.4 Using Omics Technologies Assist to Discover New Intervention Targets?

6.4.1 Genome and Transcriptome Analysis

Drug discovery is far less advanced for *S. scabiei* than for other parasites. Indications of novel targets might come from mining multi-omic databases. Mining might aim to identify extracellular molecules that ideally (1) have an activity that can be modulated by a drug, (2) are unique and essential to parasite life and survival or (3) underpin parasite-specific reproductive or disease processes.

Recent advances in nucleic acid sequencing, proteomic analyses and bioinformatics technologies have enabled a remarkable number of arthropod genomes to be decoded (e.g., [56, 57]). While the recently established draft genomes provide resources to start exploring arthropods at the genomic level, the transcription/expression profiles and the functions of most genes of acarines are still largely unidentified. Some researchers have begun to use genome sequences to assist in studying the expression, localisation and function of genes employing RNA sequencing [58, 59] and proteomics tools [60], but this field is still in its early stages.

RNA (transcriptomic) sequencing quantifies particular types of transcripts, such as total RNA, polyadenylated RNA and small RNAs from whole organisms, or from specific developmental stages or tissues. The technology is very useful to understand for example, which genes are transcribed at what stage of the parasite life cycle or which pathways may be disrupted due to a particular treatment. Respectively, proteomics allows to identify proteins that are up- or down-regulated, for example during specific developmental stages, in particular tissues of the parasite or as a result of treatment with a drug. The International Nucleotide Sequence Database Collaboration (INSDC) database (via http://i5k.github.io/arthropod_genomes_at_ncbi), InsectBase (http://www.insect-genome.com/) and FlyBase (https://flybase.

org/) are useful resources to explore and mine such arthropod data and to use the functional and structural genomic information to understand biology.

Some recent acarine genome-sequencing projects have produced significant amounts of data on mites [1, 7, 27, 40, 46]. However, a critical analysis of the literature reveals that (a) most genomes are drafts and, thus, are fragmented; (b) only a small part of a genome codes for proteins; (c) a large number of proteins encoded in the genome are orphans (unknown) and (d) most of the genome is DNA that we know nothing about (and is thus called 'dark matter'), but we expect that this matter will have crucial functional and regulatory roles [61]. It should soon be feasible to search the model organism Encyclopedia of DNA Elements (modENCODE) project [62] to identify highly significant functional and regulatory elements that control the expression of genes involved in pathways that influence the physiology, biochemistry and behaviour (phenotype) of mites, and their tissues and cells. Exploration of the structure and function of unique genes/gene families in *S. scabiei* and related mites has already begun and may identify critical molecular mechanisms linked to parasitism and the pathogenesis of scabies.

A determining prerequisite for future molecular work, though, will be to sequence the genomes of representative biovars of *S. scabiei* (e.g., from human, pig and canids) to chromosome-scale contiguity. To do this, an automated bioinformatic pipeline could be used to assemble both long- and short-read sequence data sets [63], and accurately predict the genes [64]. Using complete mite genomes, tandem multi-gene families that are crucial to understanding *S. scabiei*-specific traits of biological importance (e.g., adaptation, parasitism, fitness, virulence, pathogenicity and drug resistance) could be identified.

6.4.2 Gene Silencing and Non-Coding RNAs

The roles and functions of orphan scabies mite proteins could be investigated by targeted gene-silencing, using either double-stranded RNA interference (RNAi) [65] or a clustered regularly interspaced short palindromic repeats (CRISPR)-based approach [66]. While establishment of the first methodology is underway, CRISPR has not been reported for scabies parasites.

RNA interference is a biological process of gene expression regulation in almost all the eukaryotes and in some prokaryotes. In eukaryotes, mainly the microRNA (miRNA) and small interfering RNA (siRNA) initiates the RNAi machinery [67, 68]. This mechanism has been used experimentally in functional genomics, therapeutics and in biotechnology in varying capacities. An organism should have minimum of one *Argonaute*-like polypeptide, one *Piwi*-like protein, one *Dicer* and one RNA-dependent RNA polymerase to have functional RNAi system [69]. In recent years, presence of RNAi system in *S. scabiei* mites was proven in genomic and functional levels [70, 71].

Principally, primary microRNAs (pri-miRNAs) are transcribed from the microRNA (miRNA) genes in the nucleus which are then processed by *Drosha* (nuclear RNase III) to release pre-miRNAs. *Exportin* releases these pre-microRNA

into the cytoplasm which are then excises by the ribonuclease III enzyme *Dicer* to small RNAs (siRNA) [72]. In addition, RNA-dependent RNA polymerase *(RdRP)* amplifies the miRNA to produce *dsRNA* which is also then cleaved by *Dicer* to produce siRNA [73]. Generation of active short interfering RNA initiates the RNAi pathway. This process consists of cofactor dsRNA-binding domain proteins (dsRBD): *Pasha, Loquacious* and *R2D2*, and proteins with RNA binding and nuclease activity; *VIG, Piwi* and *C3PO*. Assembly of RNA-induced silencing complex (RISC) and unwound siRNA with mRNA causes the siRNA mediated nucleolytic degradation of the targeted mRNA by the RNaseH enzyme *Argonaute* causing translational gene silencing [72, 74]. Genomic and transcriptomic analyses of *S. scabiei* identified 29 genes homologous to core components of RNAi pathways including *Exportin, Drosha, Dicer, Pasha, Loquacious, Argonaute, RdRP* and *VIG* [70, 71]. However, the systemic RNAi detective gene *(sid)*, synthetic secondary siRNA-deficient Argonaute mutant (*sago*), the RNAi spreading detective gene (*rsd*), *Piwi* and *C3PO*, which were detected in nematodes, *D. melanogaster* and *T. urticae* were not reported to be present in the in *S. scabiei* genome [70, 71]. Even though the *sid*, *sago* and *rsd* genes which are important for systemic RNAi machinery are absent, the presence of *RdRP* for the endogenous synthetic secondary siRNA production suggest a potential novel RNAi spreading mechanism in *S. scabiei* [71]. Functional analysis of *S. scabiei* RNAi machinery has used the housekeeping gene *Ss*GST-*mu1* and 40% reduction of its expression was shown upon *S. scabiei* emersion in *Ss*GST-*mu1* dsRNA [70], compared to the control, *E. coli* LacZ dsRNA immersed mites.

Given that RNAi has been shown to work in *S. scabiei* [70, 75], panels of *S. scabiei*-specific genes of interest could be tested for their essentiality to mite survival. In parallel, high-resolution imaging could be used to identify non-wildtype phenotypes (e.g., motility, lethality or developmental defects), and knock-down specificity could be confirmed by transcriptomics and proteomics. Such a focus could provide an avenue to identify and characterise essential, *S. scabiei*-specific genes as drug targets.

Distinct developmental stages of *S. scabiei* are proposed to secrete microRNAs, some of which likely exert immunomodulatory effects on their mammalian hosts and/or govern the host–parasite interplay [33]. We need to further our understanding of these mechanisms and should systematically and comprehensively define microRNAs and other non-coding RNAs present in the *S. scabiei* genome, and then determine the subset of non-coding RNAs that contribute directly to parasitism. Although these are challenging tasks, the outcomes here could lead to a significant shift in our understanding of scabies mite biology at the molecular level, which would likely enable the discovery and development of new interventions.

6.5 Conclusion

It is hoped that deciphering the scabies mite genome will accelerate research into scabies. This has occurred in the aftermath of many genome projects for other infectious agents. Clearly, multi-omics approaches being established for eukaryotic

pathogens should be applicable to exploring scabies mites at the molecular level, and to elucidate host–parasite interactions and disease processes.

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Scabies-Associated Microbiota

7

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7.1 Why Should We Be Interested in Understanding the Microbiota Changes in the Context of Healthy Versus Diseased Skin?

7.1.1 The Skin Is a Dynamic Microenvironment

The epidermis has evolved as the outer layer of all higher vertebrates. It is a multilayered epithelium, with its outer layers being gradually reinforced with keratin and subsequently dying to form a dense outmost matrix. It is crucial for survival in providing an upper relatively cool, dry, high-salt, hydrophobic and acidic barrier that is inhospitable for microbes [1]. Epidermal skin layers continuously renew through the process of epidermal differentiation [2] and this desquamation process continuously eliminates potential microbial intruders. Nevertheless, countless species of microbes manage to grow on the skin surface, within skin invaginations and appendages such as glands and hair follicles, and some are even detectable within the dermis and the dermal adipose tissue [3]. Likely, the vertebrate cutaneous surface is, apart from the vertebrate intestinal system, the most populated organ of the human body as it is inhabited by estimated trillions of bacteria, archea, viruses, fungi and small arthropods. These microbial communities, the skin microbiota (i.e.,

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the assemblage of microorganisms existing on human skin), influence the host's health and disease in intricate ways. Many of these microbes coexist with their host in a commensal or even mutually beneficial relationship, some are known to switch roles and become pathogenic and some are outright harmful to humans. Over several decades, dermatologists and microbiologists have addressed basic questions regarding the complex microbial skin population – how it is composed, how it changes in response to environmental changes, how it interacts with the immune system, how its diversity contributes to health and disease status, how it changes during disease and how it is impacted by treatment.

Recent research has highlighted that changes in the skin bacteriome diversity are associated with common dermatologic conditions such as atopic dermatitis, acne, psoriasis and rosacea [4]. In the latter microscopic mites seem to play a role. The mite *Demodex folliculorum* normally lives in in small numbers in the sebaceous glands of healthy human skin, but is found in excess on the facial skin of rosacea patients [5–8]. It has been postulated that the chitin within the mite exoskeleton stimulates keratinocytes and thereby modulates the innate immune response of the skin by upregulating secretion of cytokines and chemokines [9]. The demodex mites are unlikely the only cutaneous agent contributing to rosacea. It has been shown that while treatment with topical anti-demodex cream (5% permethrin) decreased demodex mite counts significantly, it was not superior to topical antibiotics (metronidazole 0.75%) in improving rosacea, suggesting that bacterial pathogens are involved [10]. Host related factors like genetic aetiology, immune system dysregulation, abnormal neurological and vascular signalling and dietary triggers may contribute to the dysbiosis of skin microbiota, which ultimately leads to skin sensitivity and inflammation. Demodex mites are thought to be carriers of *Bacillus oleronius* [11–13] and beta-haemolytic *Staphylococcus epidermidis* with increased virulence [14].

Similarly, there may be a distinct scabies mite-associated microbiota contributing to the establishment of secondary infections and potentially to serious sequelae of scabies infection. The bacteria that come with scabies mites could be an important aspect to understand the parasite's biology and scabies disease progression.

7.1.2 The Microenvironment of the Scabies Mite

Scabies mites burrow into the upper epidermis. They manage to evade separation from the host through desquamation by persevering and feeding within the moist and nutritious lower stratum lucidum, granulosum and spinosum. They cannot reside in more outer epidermal layers, seemingly because they would desiccate and starve. They do not go deeper, presumably to avoid host defence. The particular mechanisms allowing the mites to maintain themselves in the border area of alive and dying epidermal cell layers are still unknown; however, for *P. ovis* infestation,

evidence of a potentially deleterious effect of mite allergens on epidermal differentiation has been recently provided [15].

It is also unknown how the mite deals with the huge variety of bacteria, fungi and viruses it encounters on the skin surface. An amazing number of approximately one billion bacteria have been estimated to inhabit a typical square centimetre of human skin [16], consisting of resident and transient microbes, many of those being both commensals and opportunistic pathogens, and taking on shifting roles, ranging from host-beneficial to pathogenic, depending on the situation. When the mite breaks through the upper epidermal matrix some of these microbes may enter as well or may be carried in with the mite (Fig. 7.1a). In addition, the intense pruritus typical for scabies mite infestation causes scratching which provides further access of microbes into the skin. Finally, scabies mites modulate the microenvironment within the epidermis by releasing a multitude of mite proteins into the skin (Fig. 7.1b), which will be discussed in more detail below. These changes may be favoured by some microbes.

Traditionally scabies infestation was plainly viewed as a nuisance, a relatively harmless nocturnal itch caused by an external ectoparasite. A connection with severe and systemic downstream complications due to secondary bacterial infections has only recently been discussed [17, 18]. More and more evidence is emerging that, especially in tropical climates, the real threat of scabies are the bacteria that come with the mite.

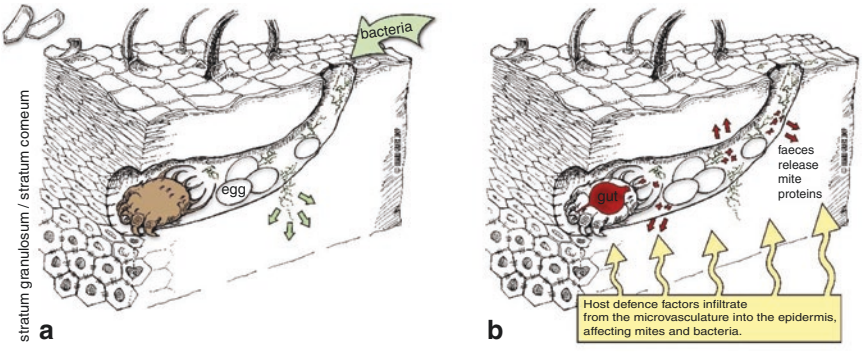


Fig. 7.1 (**a**) Mite infection allows bacteria into the burrow. Mites open the epidermal matrix, burrow through the outermost layers and reside in the deeper epidermal layers to feed on serous material and replenish water. This allows entry for microbes from the surface into the burrows. (**b**) Among the host proteins ingested by scabies mites, host defence proteins such as immunoglobulins and complement factors are potentially detrimental to the mite. To counteract host defence, the mite releases proteins that supress inflammation. This modulation of the microenvironment within the confined space of the epidermal burrows may cause a change in the local microbiota

7.2 What Do We Know About Microbes Associated with Scabies?

7.2.1 Epidemiology

Scabies (common and severe forms) is among the common dermatological conditions worldwide [19, 20], leading to high disease burden in resource-poor populations. Scabies lesions often facilitate bacterial skin infections [21], causing pyoderma, cellulitis, sepsis, acute rheumatic fever, rheumatic heart disease and acute post-streptococcal glomerulonephritis (APSGN) (Fig. 7.2). In scabies-endemic tropical locations [21–25], scabies is a key underlying factor of secondary bacterial infections with *Streptococcus pyogenes* and/or *Staphylococcus aureus* (Fig. 7.2). Very high rates of complicated skin-borne infections with these pathogens are reported in Indigenous Australians [26–28], and the situation is likely similar in other resource poor settings globally. This association is supported by evidence from the Solomon Islands and Fiji, where acaricidal ivermectin treatment alone resulted in a highly significant decrease in haematuria (marker of APSGN) [29] and impetigo [30], and was similarly effective to a combined treatment of ivermectin and antibiotics [31].

7.2.2 Pig In Vivo and Ex Vivo Studies

A longitudinal study using a porcine model [34] showed a substantial impact of mite infection on the healthy skin microbiota, with a dramatic shift from commensal to pathogenic *Staphylococci* and a decrease in beneficial *Lactobacilli* [34]. Importantly, acaricide treatment eliminated the mites but did not restore the healthy microbiota.

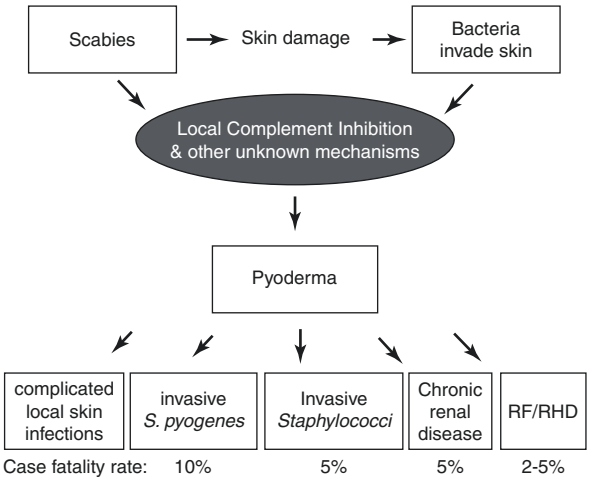


Fig. 7.2 Complexity and impact of scabies [32, 33]. Skin damage allows entry of mite and bacteria, which persist due to a range of mechanisms. Consequently, scabies infected skin is prone to bacterial infections, potentially, causing pyoderma, cellulitis, sepsis, acute rheumatic fever, rheumatic heart disease and acute post-streptococcal glomerulonephritis (APSGN)

It is unknown whether the scabies mite requires endosymbionts for survival. Initial investigations failed to detect genes encoding *Wolbachia* surface proteins and specific 16S rRNA in pig mites [35]. A later study confirmed the absence of *Wolbachia* in scabies mites and found *Streptomyces* being present in the mite gut [36]. Identifying symbiotic bacteria essential for *S. scabiei* could lead to new therapeutics. A trial for the treatment of skin sores in children undertaken in Northern Australia, tested oral cotrimoxazole to treat impetigo [37]. Intriguingly, cotrimoxazole-treated children who were diagnosed with scabies, showed a more rapid improvement of skin lesions than those without scabies. Cotrimoxazole might affect the microbiota within the mite, as it is thought to explain the successful treatment of head lice in this way [38]. This fascinating example indicates that more information is needed to assess the roles that mite symbionts play.

7.2.3 In Vitro Studies Reveal Molecular Interactions Between Host, Mite and Bacteria

Mechanical interference with skin integrity by mite burrowing and host scratching disrupts the skin barrier and serves as an entry point for bacteria (Fig. 7.1a). In addition, experimental in vitro [33, 36, 39] biochemical and molecular data show that the mite creates a protective microhabitat, thereby facilitating the proliferation of opportunistic pathogens (Fig. 7.1b). Scabies mites secrete/excrete complement inhibitors that locally suppress the host's innate immune response [18, 33, 36, 39–43] and simultaneously promote the growth of *S. aureus* [39] and *S. pyogenes* [36] in the skin. Other examples are numerous digestive mite proteases [44–48] which damage the host epidermis, causing pruritus and inflammation. Some of the molecules released by the mites have even been found in the dermis (Fernando et al. in review). It appears that the scabies mite has evolved multiple classes of proteins to enable its parasitic lifestyle and assist co-infecting microbes through protocooperation.

7.2.4 Histology

Early scanning electron microscopy provided first direct evidence of extensive bacterial colonisation of scabies burrows in scabetic skin crusts [49] and more recent electron microscopic imaging showed various microbes on mites and faeces (Fig. 7.3).

Bacterial cultures grown from mite faeces isolated from human skin scrapings revealed haemolytic *Staphylococcus aureus* [49]. Recently, preliminary pilot metagenome sequencing data of the microbes associated with human mites from two Australian patients, obtained as part of the ongoing mite genome project [50], indicated an abundance and large variety of opportunistic pathogens (unpublished).

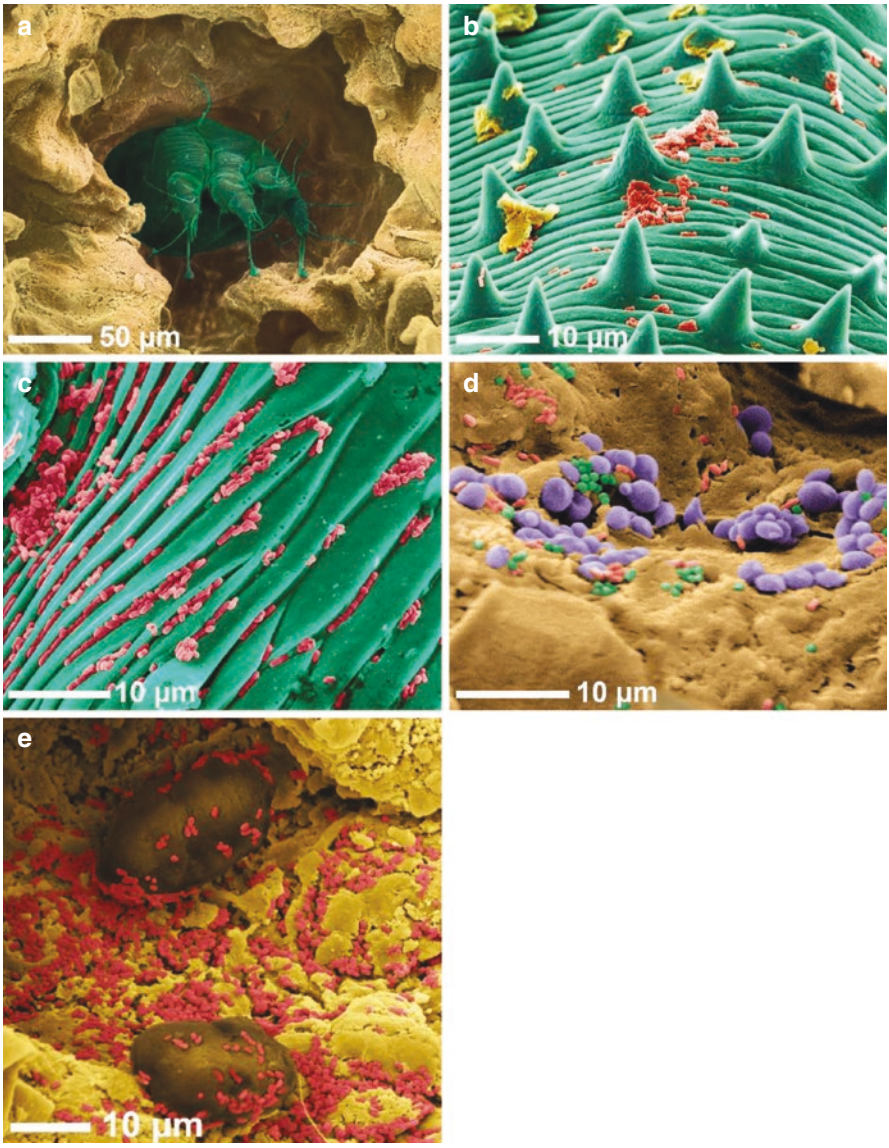
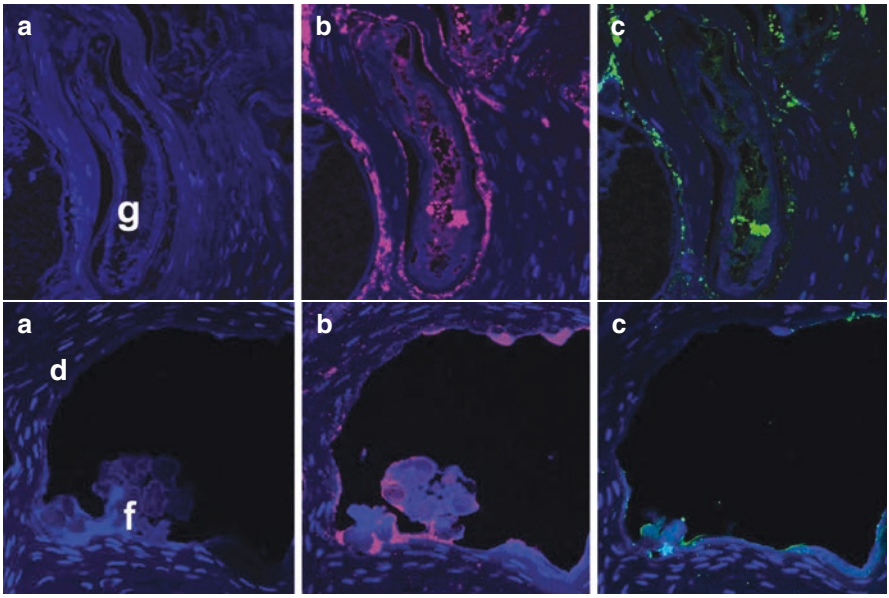


Fig. 7.3 Scanning electron microscopy featuring a mite (**a**), and various microbes (**b**–**e**). Mite-associated microbiota are seen on the mite surface (**b**, **c**), in the burrow (**d**, **e**) and on faecal pellets (**e**)

Using bacteria species-specific antibodies the presence of *Staphylococcus aureus* and *Streptococcus pyogenes* in the gut of scabies mites as well as in their faeces was confirmed (Figs. 7.4 and 7.5). The presence of the potential mite endosymbiont *Streptomyces* in the mite gut was demonstrated histologically by FISH analysis [36].



Figs. 7.4 and 7.5 Immunohistological localisation of *Staphylococcus aureus* and *Streptococcus pyogenes* in the scabies mite gut (*g*, Fig. 7.4 **a**–**c**) and excreted mite faeces (*f*, Fig. 7.5 **a**–**c**) using confocal microscopy. Probing consecutive histological sections of human scabies infected skin with bacteria species-specific antibodies indicates the presence of *S. aureus* in pink (**b**) and of *S. pyogenes* in green (**c**), whereas the no primary antibody negative control shows no bacteria-specific staining (**a**)

7.3 Research Questions, Methodologies and Challenges

7.3.1 Research Questions

There is no immediate solution to achieve a lasting reduction of the significant burden attributable to scabies and associated bacterial diseases. Currently, little is known about scabies-associated pathogens, even though they are the major cause of morbidity and mortality [17]. A fundamental problem is that the molecular biology of the scabies mite is very poorly understood, compared to other parasites. Scabies mites cannot be cultured and most patients presenting with common scabies have <20 mites on their body and so are not suitable mite-donors for in vitro experiments. Preliminary mite genomic data [50–52] and in-depth pig mite PacBio/transcriptome/proteome analyses *(Korhonen* et al.*, in review)* have been generated, but very little is known about the tripartite interactions between the parasite, associated bacteria and the human host. Key research questions include: Which bacteria have more than an 'opportunistic' link to *S. scabiei*? Through which mechanisms do mites and bacteria protect themselves against and affect host defences? Do proportions of disease-causing bacteria differ in patient populations? Does the mite act as a carrier

of bacterial pathogens? Does it rely on symbiotic bacteria and could these be a therapeutic target? Deciphering the microbiome in both common and crusted scabies would allow us to address these questions and would accelerate biomedical research into the scabies disease complex, thus enabling development of better strategies for diagnosis and treatment.

As for other microbiota surveys the goal of a scabies microbiota project will be to identify individual taxa (genera, species and strains) and community features, such as diversity, that are associated with the presence of scabies mites. Profiling the scabies-associated microbiota may enable scientists to establish causation and dissect molecular and biochemical mechanisms between host, parasitic mites and microbes. Clarifying which modifications and disturbances scabies causes to the healthy skin microbiota will provide essential information to the clinical question whether and when acaricidal treatment should be combined with antimicrobial treatment. While the ongoing scabies genome project represents a logical strategy for identifying novel diagnostic and drug targets in the mite, the link to secondary infections may represent a previously unrecognised Achilles heel of the parasite, i.e., mite-associated microbes themselves may serve as diagnostic and/or therapeutic targets.

7.3.2 What Methodologies Can Be Used to Study the Scabies-Associated Microbiota?

7.3.2.1 Animal Model Versus Human Studies

Animal models, among them our porcine model, have helped us to advance knowledge in many areas of scabies biology [50, 51, 53–62] and gave a clear indication of the relevance of the scabies microbiota [34], but these cannot adequately recapitulate the human skin microenvironment.

Exploring the human mite-associated microbiota in geographically distinct locations with differences in climate and socioeconomics will clarify many aspects of the role of scabies mites in the transmission and pathogenesis of secondary bacterial infections.

Some specific research aims were recently proposed:

Microbial profiling of common scabies samples from different geographic locations and socioeconomic situations may provide detailed insight into the microbes associated with common human scabies. Longitudinal microbial profiling in human patients during acaricide treatment may determine whether current scabies treatments restore healthy skin microbiota or whether additional antibiotic treatment are required. Mite material derived from severe scabies cases with high parasite loads will also allow the investigation of the mite internal microbiome. It may be possible to identify candidate symbionts in scabies mites from humans and to assess their potential as targets for therapeutics or surrogate diagnostic markers.

7.3.2.2 Methodologies of Molecular Data Generation

Culture-Based Investigations

Historically, culture-based approaches have been the standard for characterising microbial diversity, but only a minority of bacteria are able to grow in culture and these are neither the most abundant nor the most influential organisms among the real-life microbiota [49].

16S and ITS 1 Sequencing

Skin microbes are adapted to a cool, dry and acidic and often anaerobic environment and hence many will not thrive under routine culture conditions. The development of molecular techniques to identify and quantify microbial organisms has revolutionised this research area [63]. Importantly, an organism does not need to be cultured to determine its type by sequencing.

With the increasing recognition of the importance of the human microbiome next generation sequencing and analytic tools have been developed to characterise microbial populations in specific habitats. Importantly, these methods eliminate biases associated with isolating and culturing microorganisms. Amplicon-based sequencing, i.e., PCR amplification and sequencing of specific parts of the bacterial chromosome, is the most common strategy and has been extensively employed to characterise microbiota profiles. Mostly the highly conserved 16S ribosomal RNA (rRNA) gene is targeted, which contains highly variable regions that allow us to distinguish different bacterial taxa. For the analysis of fungal communities, regions of DNA between the 18S, 5.8S and 28S rRNA genes, termed internal transcribed spacers (ITS), contain both hypervariable regions and conserved regions for taxonomic identification and primer annealing, respectively. From the data generated, similar sequences can be grouped into operational taxonomic units (OTUs), statistically analysed and graphically represented.

Whole-Genome Shotgun Metagenomics

If sample size allows, metagenomics shotgun sequencing allows better taxonomic and functional annotation of skin microbiota. It captures all microbes present (bacteria, fungi, viruses and archea), as it reveals genes and, depending on the sequencing depth, potentially genomes of the organisms present and allows strain level resolution. Whole-metagenome shotgun data are randomly fragmented and the assembled into contigs. Taxonomy is assigned and gene content predicted, and enrichment analysis allows the prediction of metabolic and genetic pathways.

Metatranscriptomics and metaproteomics are the most recent breakthroughs of the next-generation sequencing technologies. These not only provide information about the taxonomic structure of the microorganisms present in a sample, but offer valuable information regarding the expression of microbial genes over time, i.e., during the course of a disease. When combined with metagenomics, they would provide a more comprehensive picture. Thereby the active functional profile of a microbial community is revealed.

7.3.3 Possible Pitfalls

The following limitations of new generation sequencing approaches have been recognised specifically for skin microbiota studies [63]: Skin samples are commonly either swabs or scrapings and as such typically low in biomass and consequently extremely susceptible to reagent and environmental contamination, which produces false-positive results. While culture-independent approaches capture a better snapshot of the microorganisms present in a sample, they cannot distinguish live versus dead microorganisms. The sequencing data obtained are associative, and additional experiments are required to show causality. Many analytical approaches require reference data sets, which are still very limited for skin microbes. Consequently, uncharacterised microbes can currently not be assessed.

7.3.3.1 Essential Patient Numbers

Scabies is generally not reportable and patients often do not present to clinics. Similarly, impetigo is generally not seen as a reason to visit the doctor. Crusted scabies is an extremely rare condition that patients often endure for a very long time before presenting to the clinic. Thus, it is a significant task to find and recruit appropriate numbers of cases for this research.

7.3.3.2 Confounding Factors

The collection technique can profoundly influence microbiota study results and must be kept the same throughout a study. The importance of consistent collection techniques was recently discussed [64]. Similarly, DNA extraction techniques as well as sequencing and analysis protocols must be consistent to allow analysis across studies.

Negative controls for every step of the protocol are a crucial because they allow assessment of background contamination from reagents and the environment [65]. Sequencing of a mock community as a positive control, containing microbial DNA from known organisms in known quantities, allows an independent testing of the experimental procedures.

Apart from scabies infestation, other factors influence the skin microbiota and may be confounding factors. For example, samples from patients that were treated with systemic or topical antimicrobials must be excluded. Recording demographics, medical history and topical/systemic medications will be essential information when evaluating microbiome data. The criteria for identifying healthy individuals and for disease phenotyping (validated diagnostic criteria [66, 67], severity scoring and clinical photography) must be clearly defined. Data collected should include age, sex, antibiotic use, pet ownership, skin product usage, physical activities, profession, ethnicity and season. Careful sampling site selection is essential, as the skin microbiota changes with skin topography [68, 69]. Several studies have examined the variability of the skin bacterial microbiome in and between individual subjects and over time. When comparing contra-lateral sites

(left and right), low intra-individual variability was reported [70–72]. It may be useful to examine scabies-typical body sites including control samples from corresponding co- and contra-lateral healthy sites, to assess both the mite-affected and the neighbouring site-specific microflora. Sampling healthy individuals on scabies-typical body sites will be informative as well. Data analysis on three levels—site specific, intra-individual and inter-individual—will be helpful to assess the significant variability in the skin microbiome between individuals and body sites.

7.4 Conclusion

Scabies is one of the most common skin infections and often leads to potentially harmful complications due to bacterial infections. The relationships between the human host, microbial pathogens and the scabies mite are poorly researched.

Biological networks have long been used to study interactions between biological entities. Now we have the tools to assess microbiomes in the healthy or the diseased state. This opens up completely new avenues to understand diseases. Skin microbiota and its role in cutaneous health and disease can now be investigated, due to recent advances in next-generation sequencing platforms that enable high-throughput, culture-independent detection of bacteria, fungi and viruses.

The low bioburden of the skin is currently still limiting some microbiota techniques such as metatranscriptomics, which would allow the assessment of transcriptionally active (i.e., alive) microbiota. Because many of the analytical approaches require reference genomes, future efforts should focus on building comprehensive reference databases of skin-specific microbes, including yeasts, bacteria, viruses and micro-eukaryotes such as mites.

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Experimental Animal Models

8

Charlotte Bernigaud, Gangi Samarawickrama, Jacques Guillot, and Katja Fischer

8.1 Introduction

Human scabies is a widespread disease in both wealthy and low- and middle-income countries [1–3]. It is a parasitic skin disease affecting various mammalian animals including humans due to the mite *Sarcoptes scabiei* [4–6]. It is called sarcoptic mange in animals. Common animal hosts are dogs, rabbits, pigs and several wild mammals [7–10] (see Chap. 22). Despite the recognised burden of scabies or sarcoptic mange, the dedicated means to study the disease are low. Indeed, the scientific understanding of the disease, such as pathogenesis or immunology is not well appreciated. There are

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no molecular diagnosis tools, no effective therapeutic intervention and poor understanding of the prevention of the contamination. Research has been curbed for many years, by poor access to the parasites. Scabies has always been difficult to study. It is a tiny parasite (0.3 to 0.5 mm for the larger female adult), including five to seven different developmental stages (three egg stages, larvae, protonymphs and adults) [11]. Immature forms and adult males are difficult to distinguish; only the adult females are easy to recognised, due to their bigger size [11]. It is very difficult to isolate parasites in large quantities from humans. Most of the clinical manifestations are common or not severe conditions, and during a typical infestation, the mite load is often low (5 to 10 parasites per host) [1, 2]. Occasionally, large numbers of mites can be obtained from an hyper-infested patient with crusted scabies, but for ethical reasons and practicability, extensive research studies can't be performed easily [12]. Furthermore, the parasite is difficult to study as motile stages cannot survive outside their host for more than 48–72 h to a few days depending on temperature and humidity [13] and cannot be cultivated in vitro [14–17]. Eggs may hatch but will not propagate any further.

Thus, the availability of a tractable animal model allowing ample proliferation of parasites is necessary. The establishment of an experimental model makes it possible to carry out preclinical studies that can compare the acaricidal activity of new treatments, but also fundamental studies to better understand the cycle and survival of the parasite. In this chapter, we present the different existing animal models, their limitations and their advantages.

8.2 Existing Animal Models

To date, four different animal models have been successfully established and are available for studying the features of the biology of the mite, the host–parasite interactions, immunology and pathology and for performing preclinical studies that can compare the acaricidal activity of new treatments. Existing experimental animal models for scabies are summarised in Fig. 8.1.

The first experimental model to be established was a canine/rabbit model developed by Arlian et al. in the United States in the 1980s [16, 18]. They experimentally transferred *Sarcoptes scabiei* var. *canis* to New Zealand White rabbits (*Oryctolagus cuniculi*). Naturally-infected dogs were immunosuppressed with azathioprine and prednisolone. Heavily infected crusts from the dogs were placed on the shaved back of a rabbit for 12 to 22 h [16, 18]. A plastic Petri dish covered the crusts and was fastened by tape. Among 23 experimentally infected rabbits, 6 animals established permanent infection with a single inoculation, while 10 and 7 rabbits developed with a temporary infection of 1 to 5 weeks and 5 to 8 weeks, respectively. Some of the latter rabbits developed a permanent infection when re-exposed, but 5 rabbits did not develop a permanent infection even after secondary exposure. Twenty-four hours after exposure in all exposed rabbits, red papules and general erythema were observed in the primary area of infection. Within 2 weeks, skin scaling became evident on the rabbits that developed permanent infections. Heavy crusts formed during the subsequent 4 to 8 weeks and the lesions and crusts gradually spread from the inoculation area over the entire body, with heavy involvement of ears, nose, face, feet and back [16, 18].

	Origin of mites	Animal Model	Contamination model	Caracteristics of *Sarcoptes* infection
Sheahan *et al.* 1974			• Infected crusts in direct contact with ear canals	• No IS needed • Tempory infestation
Arlian *et al.* 1984	 + IS		• Infected crusts in direct contact with skin (back)	• Tempory infestation • Crusts observed
Mounsey *et al.* 2010 **Bernigaud *et al.* 2016**		 + IS	• Infected crusts in direct contact with ear canals	• Stable and durable infestation • Crusts observed
Casais *et al.* 2014			• Animals in direct contacts with each other • Infected crusts in contact with skin (hind limbs)	• No IS needed • Crusts observed (less when animals in contact)
Xu *et al.* 2018 **Wei *et al.* 2019**			• Infected crusts in direct contact with skin (hind limbs)	• No IS needed • Crusts observed
Sharaf *et al.* 2020			• Infected crusts in direct contact with ear canals	• No IS needed

Fig. 8.1 Summary of available animal models for studying *Sarcoptes* infection. *IS* means immunosuppression

Several attempts were necessary to set up a reproducible model and it was difficult to obtain an infection that was stable and durable over time. Although, previous evidence suggested that a host response to an initial infection can be protective against subsequent challenge. That was confirmed in an experimental infection in sheep (*Sarcoptes scabiei* var. *ovis*) and could explain the difficulties to maintain a stable infection over time [19]. In the literature, animals that recovered from a first *Sarcoptes* infection harboured a reduced number of mites upon a second or subsequent re-infections [20, 21]. However, in Iberian ibex (*Capra pyrenaica*), this response appeared to vary with the host sex [22]; and controversially, vaccination with soluble *Sarcoptes*-mite proteins in goats [23] and with recombinant mite tropomyosin in rabbits [24] both failed to protect against subsequent infection. While the above model gave rise to a considerable list of research findings (listed in Table 8.1), the potential impact of the non-natural host on host–parasite interactions is unknown and an optimised model was needed to permit a stable and durable infection.

Natural host animal models have been secondarily developed. In 2004–2010, an Australian research team [25] used *S. scabiei* var. *suis* and its natural porcine host. Crusts with a large amount of mites were harvested from naturally-infected pigs and dissected into small pieces. Crusts were inserted deep into both ear canals of naive 2- to 3-week-old piglets. In order to maintain and propagate the infection, a synthetic glucocorticoids dexamethasone of 0.2 mg/kg/day was given to piglets 1 week prior to infection and for their entire lifespan. It takes several weeks for piglets to develop skin lesions similar to those of a natural infection. To spread and prolong the infection, immunosuppression seems necessary. Mounsey et al. observed that naturally-infected pigs self-cured over time [25]. Several years before, Sheahan

Table 8.1 List and details of published research projects within the past decade that used experimental scabies model

Publication title	Year	Animal model	Research topic	Main results	Study type	Reference
Experimental *Sarcoptes scabiei* infection in pigs: Clinical signs and significance of infection	1974	Pig	Establishment of an animal model	Experimentation of a scabies infection in a pig model	In vivo	[26]
Cross infestivity of *Sarcoptes scabiei*	1984	Dog/rabbit	Establishment of an animal model	Transfer of canine mites to rabbits—Establishment of the canine/rabbit scabies model	In vivo	[18]
Survival and infectivity of *Sarcoptes scabiei* var. *canis* and var. *hominis*	1984	Dog/rabbit	Biology of *S. scabiei*	Testing of the survival of scabies mites outside of the host	In vitro	[16]
Host-seeking behaviour of *Sarcoptes scabiei*	1984	Dog/rabbit	Biology of *S. scabiei*	Describe the response of the mite to thermal and host odour stimuli	In vitro	[57]
Water balance and nutrient procurement of *Sarcoptes scabiei* var. *canis* (Acari: Sarcoptidae)	1988	Dog/rabbit	Biology of *S. scabiei*	Describe mechanisms involved in maintaining water balance	Ex vivo	[58]
Life cycle of *Sarcoptes scabiei* var. *canis*	1988	Dog/rabbit	Biology of *S. scabiei*	Investigation of the life cycle of scabies mite (canine strain) in vivo using the canine/rabbit scabies model	In vivo	[16]
A tractable experimental model for study of human and animal scabies	2010	Pig	Establishment of an animal model	Establishment of porcine in vivo model for scabies	In vivo	[25]
Acaricidal activity of eugenol based compounds against scabies mites	2010	Pig	Drug experiment	Natural compounds tested on isolated pig mites and dog mites	In vitro	[59]

An exploratory study to assess the activity of the acarine growth inhibitor, fluazuron, against *Sarcoptes scabiei* infestation in pigs	2012	Pig	Drug experiment	Testing fluazuron in the porcine in vivo model	In vivo	[60]
Quantitative PCR-based genome size estimation of the astigmatid mites *Sarcoptes scabiei*, *Psoroptes ovis* and *Dermatophagoides pteronyssinus*	2012	Pig	Molecular biology	*Sarcoptes scabiei* genome size estimation using quantitative real-time PCR	In vitro	[61]
Antibody responses to *Sarcoptes scabiei* apolipoprotein in a porcine model: Relevance to immunodiagnosis of recent infection	2013	Pig	Immunology	Utilising the porcine model to prospectively compare specific antibody responses to a primary infection by ELISA to support the development of recombinant antigen-based immunodiagnostic tests	In vitro	[62]
Crusted scabies is associated with increased IL-17 secretion by skin T cells	2014	Pig	Immunology—pathophysiology	Evaluating the skin immune response to crusted scabies	In vivo	[63]
Scabies mites alter the skin microbiome and promote growth of opportunistic pathogens in a porcine model	2014	Pig	Pathophysiology	Longitudinal investigation of the scabies associated changes in the healthy skin microbiota using the porcine scabies model	Ex vivo	[64]
Prospective study in a porcine model of *Sarcoptes scabiei* indicates the association of Th2 and Th17 pathways with the clinical severity of scabies	2015	Pig	Immunology—pathophysiology	Use of porcine scabies model to understand immunopathology of crusted scabies	In vivo	[65]

(continued)

Table 8.1 (continued)

Publication title	Year	Animal model	Research topic	Main results	Study type	Reference
Genomic resources and draft assemblies of the human and porcine varieties of scabies mites, *Sarcoptes scabiei* var. *hominis* and var. *suis*	2016	Pig	Molecular biology	Human and pig mite draft reference genomes and preliminary annotation of 13,226 coding sequences	In vitro	[66]
Mitochondrial genome sequence of the scabies mite provides insight into the genetic diversity of individual scabies infections	2016	Pig	Molecular biology	Mitochondrial genome of the scabies mite and single nucleotide polymorphisms analysis to investigate the genetic diversity in individual infections	In vitro	[53]
Gene silencing by RNA interference in *Sarcoptes scabiei*: a molecular tool to identify novel therapeutic targets	2017	Pig	Molecular biology	Development of gene silencing by RNAi as a technique to functionally analyse potential therapeutic targets	In vitro	[67]
In vitro efficacy of moxidectin versus ivermectin against *Sarcoptes scabiei*	2017	Pig	Drug experiment	In vitro assays using porcine mites to compare dose requirements and efficacies of moxidectin and ivermectin	In vitro	[68]
Phylogenetic relationships, stage-specific expression and localisation of a unique family of inactive cysteine proteases in *Sarcoptes scabiei*	2018	Pig	Pathophysiology	Characterisation of a novel and unique *S. scabiei* family of intestinal cysteine proteases, present in all burrowing life stages	In vitro	[69]
How to eliminate scabies parasites from fomites—a high-throughput ex vivo experimental study	2019	Pig	Control of scabies	Large scale testing of strategies that can be used to kill scabies mites and eggs in textiles	Ex vivo	[70]

In vitro ovicidal activity of current and under-development scabicides: Which treatments kill scabies eggs?	2019	Pig	Control of scabies	Testing pure compounds and formulations on porcine mites and eggs revealing that most drugs used to treat scabies are not ovicidal	Ex vivo	[71]
High-throughput metagenome analysis of the *Sarcoptes scabiei* internal microbiota and in-situ identification of intestinal *Streptomyces* sp	2019	Pig	Pathophysiology	Analysis of female mite and egg metagenome data to identify the bacteria species present in scabies mites and eggs	In vitro	[72]
High-quality nuclear genome for *Sarcoptes scabiei*—a critical resource for a neglected parasite	2020	Pig	Molecular biology	High-quality genome (and associated transcriptome and proteome data sets) for *S. scabiei* var. *suis* using long- and short-read data sets	In vitro	[73]
Sarcoptes scabiei mites in humans are distributed into three genetically distinct clades	2015	Pig	Molecular biology	Evaluation of the genetic diversity of populations of *S. scabiei* including pig mites derived from the porcine model	In vitro	[7]
Efficacy assessment of biocides or repellents for the control of *Sarcoptes scabiei* in the environment	2015	Pig	Control of scabies	Assessment of the efficacy of biocides or repellents against *S. scabiei* var. *suis* for the environmental control of scabies	In vitro	[74]

(continued)

Table 8.1 (continued)

Publication title	Year	Animal model	Research topic	Main results	Study type	Reference
Preclinical study of single-dose moxidectin, a new oral treatment for scabies: Efficacy, safety, and pharmacokinetics compared to two-dose ivermectin in a porcine model	2016	Pig	Drug experiment	Proof of concept in vivo study demonstrating that a single moxidectin dose achieved a better and faster acaricidal efficacy than the recommended two-dose ivermectin treatment	In vivo	[32]
In vitro activity of ten essential oils against *Sarcoptes scabiei*	2016	Pig	Drug experiment	Assessment of the efficacy of ten essential oils against *S. scabiei* var. *suis*	In vitro	[75]
Efficacy and pharmacokinetics evaluation of a single oral dose of afoxolaner against *Sarcoptes scabiei* in the porcine scabies model for human infestation	2018	Pig	Drug experiment	In vivo preclinical study demonstrating that a single afoxolaner dose achieved a better and faster acaricidal efficacy than the recommended two-dose ivermectin treatment	In vivo	[33]
[Pharmacocinétique cutanée de la moxidectine et de l'ivermectine dans le modèle de gale porcine]—*in French*	2018	Pig	Drug experiment	Evaluation of the pharmacokinetics of ivermectin and moxidectin in the porcine model using non-invasive tools	In vivo	[56]
Non-histaminergic itch mediators elevated in the skin of a porcine model of scabies and of human scabies patients	2019	Pig	Pathophysiology	Identification of molecular mechanisms of scabies itch using skin biopsies from the porcine model and humans	In vitro	[76]

[Efficacité d'une forte dose d'ivermectine et d'une dose unique de moxidectine dans unmodèle porcin de gale]—*in French*	2020	Pig	Drug experiment	In vivo study demonstrating that a single moxidectin dose achieved the same acaricidal efficacy as a double ivermectin dose and a better and faster acaricidal efficacy than the recommended two-dose ivermectin treatment	In vivo	[55]
In vitro activity of beauvericin against all developmental stages of *Sarcoptes scabiei*	2020	Pig	Drug experiment	Assessment of the potential acaricidal activity of beauvericin against all stages of *S. scabiei* var. *suis* including eggs	In vitro	[77]
Primary and secondary experimental infestation of rabbits (*Oryctolagus cuniculus*) with *Sarcoptes scabiei* from a wild rabbit: Factors determining resistance to reinfestation	2014	Rabbit	Immunology	Investigation of clinical and pathological signs of scabies infection and the immune response in a rabbit animal model	In vivo	[34]
Evaluation of an ELISA using recombinant Ssλ20ΔB3 antigen for the serological diagnosis of *Sarcoptes scabiei* infestation in domestic and wild rabbits	2015	Rabbit	Immunology	Detection of antibodies in sera of experimentally infected rabbits with an ELISA-based assay	In vitro	[78]

(continued)

Table 8.1 (continued)

Publication title	Year	Animal model	Research topic	Main results	Study type	Reference
Vaccination of rabbits with immunodominant antigens from *Sarcoptes scabiei* induced high levels of humoral responses and pro-inflammatory cytokines but confers limited protection	2016	Rabbit	Immunology	Identification of *S. scabiei* immunodominant antigens and evaluation of their potential as vaccine candidates in a rabbit model	In vivo	[79]
Identification of a novel PYP-1 gene in *Sarcoptes scabiei* and its potential as a serodiagnostic candidate by indirect-ELISA	2018	Rabbit	Immunology	Evaluation of a potential serodiagnostic candidate for sarcoptic mange in rabbits using the rabbit experimental model	In vitro	[35]
Serodiagnostic potential of alpha-enolase from *Sarcoptes scabiei* and its possible role in host–mite interactions	2018	Rabbit	Immunology	Detection and evaluation of the alpha-enolase protein as a potential vaccine candidate	In vitro	[80]
Comparative analysis of host resistance to *Sarcoptes scabiei* var. *cuniculi* in two different rabbit breeds	2019	Rabbit	Immunology	Comparison of the host resistance to *S. scabiei* var. *cuniculi* of a new breed of domestic rabbit compared with that of a traditional rabbit breed	In vivo	[36]
The scabicide effect of moxidectin in vitro and in experimental animals: Parasitological, histopathological and immunological evaluation	2020	Rabbit	Drug experiment	Demonstration that a single dose of moxidectin was more effective than ivermectin in a rabbit model	In vivo	[37]

et al. made the same observation while using piglets experimentally infected with pig-derived mites. In this model, without immunosuppression, the skin lesions did not persist for more than 2 to 3 weeks [26]. In humans, it is now well known that the use of corticosteroids (topically or systemically) causes the transition from common scabies to more severe cases such as profuse and/or crusted scabies [27–29]. In addition, corticosteroids are routinely used to maintain bacterial, fungal or parasitic infections in animal models [30, 31]. Dexamethasone is therefore a key factor for the spread, stability and reproducibility of parasite infection. The pig model was transferred in 2014 in France at the veterinary College of Alfort (EnvA), France. The model was optimised to allow pre-clinical studies of new acaricides [32, 33].

In 2014, Casais et al. developed an animal model using New Zealand white rabbits experimentally infected with *S. scabiei* var. *cuniculi* isolated from a European wild rabbit [34]. The infection was permitted using two different techniques. Three-month-old New Zealand white rabbits were infected (1) by direct contact for a 24-h period with an infected rabbit or (2) by immobilising infected crusts on shaved hind limbs for 24 h. In either model no immunosuppressant was used. In the rabbits infected by direct contact, crusts appeared in 10 out of 10 rabbits 2 weeks post-infection. The crusts started at the root of the claw and then gradually propagated up to the paw, and to the ears and nostrils. In the rabbits infected with a crust sample, lesions became visible at 2 weeks post-inoculation in 2 out of 10 rabbits and spread mainly down to the claw [34]. More recently, another rabbit model was developed in China by Xu et al., who maintained *S. scabiei* var. *cuniculi* in New Zealand white rabbits [35]. Naturally infected New Zealand White rabbits from a farm were euthanised and used to collect mites. Receiver rabbits were infected by direct contact with thousands of mites accumulated in a dressing that was placed and fixed on each rabbit shaved hind limb for 24 h. Over the ten rabbits infected (5 females and 5 males), first lesions were visible 3 to 7 days post-inoculation and all rabbits developed clinical signs of *Sarcoptes* infection. Crusts were able to develop [33]. This model was further developed with slight modifications by Wei et al. [36]. Using the same procedure, a last model was developed very recently in Egypt in 2020. *Sarcoptes scabiei* var. *cuniculi* mites were isolated from naturally infected rabbits from a farm in Tanta, Egypt and transferred to naive male New Zealand white rabbits [37]. Sharaf et al. were able to perform a pre-clinical therapeutic trial comparing the acaricidal activities of moxidectin and ivermectin [37].

8.3 Relevance of the Porcine Model

Pigs are frequently used as experimental models for studying various infectious skin diseases and have been recognised as a preferred model to investigate skin diseases in translational dermatological research [38–42]. Despite high costs, pig models are often preferred over rodent models for the study of dermatological conditions [42]. The anatomy and physiology of pig skin [39] is comparable to human skin; whereas the skin of rodents differs significantly from humans as it is loosely connected to the subcutaneous connective tissue [43]. In contrast, pig and human skin are tightly attached to it [39]. Regarding the subcutaneous compartment, fat is the main

insulation component of porcine and human skin (vs. fur and hair for rodents) and food supply is provided by blood in the dermis, comparably in pigs and humans [44–46]. Moreover, the pig immune system is well described and a considerable selection of biochemical tools is available [47]. The porcine innate and adaptive immune systems are highly similar to human skin [48], and the complement system is comparable to that of humans [49]. In addition, cutaneous pharmacology, such as absorption, persistence or elimination of drugs, is comparable [50]. Therefore, many researchers favoured pigs for preclinical development of new treatments for humans [51]. Importantly, pigs are natural hosts of *S. scabiei* and present a similar epidermal, morphological and immunological skin scabies infection to that of humans [52]. Furthermore, when direct comparisons were possible, variety *suis* and variety *hominis* mites appeared to have a similar biology [13, 53].

In pigs, the ears are the most common site of *Sarcoptes* infection and are usually the primary focus from which the mite population spreads to other areas of the body, especially the back, flanks and abdomen [54]. Many pigs harbour unapparent infections throughout their lives, and the main mode of transmission appears to be between carrier sows and their piglets during suckling (see Chap. 22). Affected pigs scratch continuously, with head shaking. Common signs are papular eruptions with erythema, pruritus and hair loss. As the infection progresses, the skin becomes thickened, crusted with exudates due to damage caused by scratching [54].

A summary of advantages and challenges of using a pig model for the study of skin infectious diseases is presented in Fig. 8.2.

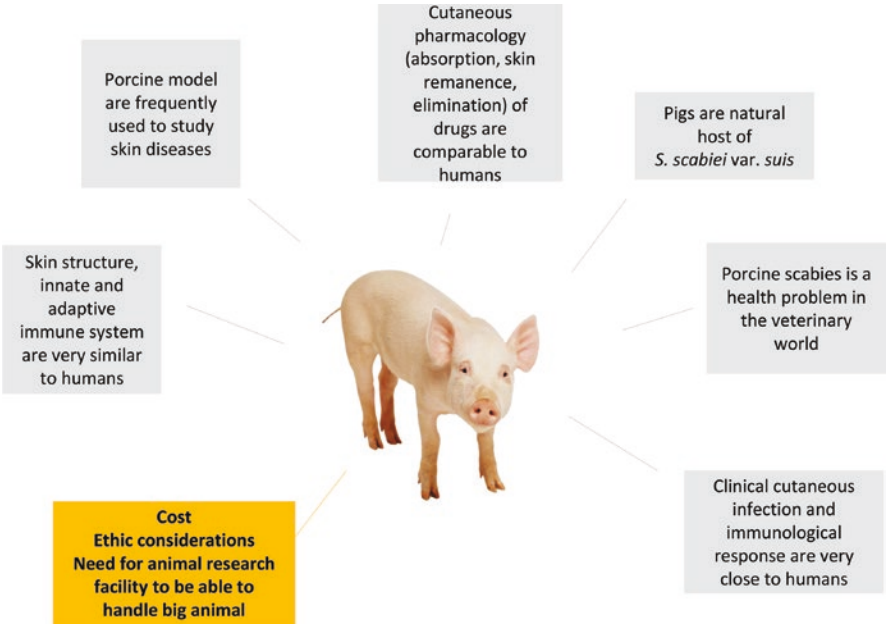

Fig. 8.2 Summary of advantages and challenges of a pig model for the study of skin infectious diseases

8.4 Development of a Pig Model to Advance Biomedical Scabies Research

The pig model was developed in the early 2000s by researchers at the QIMR Berghofer Medical Research Institute in Brisbane, Australia in collaboration with the Animal Research Institute, Yeerongpilly [25]. After extensive, but unsuccessful attempts to establish experimental infection of mites from humans, pigs and dogs in multiple mouse breeds, the research group developed an experimental porcine model that achieved high mite numbers within 6–10 weeks and a prolonged infection times of up to 6–12 months. Many pigs were resourced from Queensland backyard piggeries and infected ears were collected from abattoirs until eventually mites were successfully passaged to naive piglets. Since the establishment of today's colony in 2008, over 30 continuous cohorts of infected pigs have been maintained, first at the DEEDI Animal Research Institute, Yeerongpilly, Queensland, Australia and later at the Centre for Advanced Animal Studies, Gatton, Queensland, Australia, which is now called the Queensland Animal Science Precinct as part of the University of Queensland, Gatton.

In the first series of infections, the piglets were placed in the pens next to infected pigs from previously infected groups. A heater was placed on the fence in between the pens to promote skin to skin contact and thereby enhance and assure mite transfer between pigs and a successful infection. Subsequently, mite transmission was additionally boosted by direct transfer of mite-infected skin crusts from the infected group to the naive piglets. In the initial stages of the model it was observed that even though all pigs show early signs of *Sarcoptes* infection most of them self-cured after a few weeks. Based on observations in humans, where ordinary scabies developed in to severe crusted scabies when corticosteroids treatment is administered [27–29], a regime of oral dexamethasone treatment of the pigs, adjusted to weight gain over time, was developed. Dexamethasone treatment is routinely started 1 week post weaning and 1 week prior to infection.

The development of this model is responsible for the increased knowledge of *Sarcoptes* mite biology, host–parasite interaction and pathobiology of scabies over the last 20 years. The list of all published research projects within the past decade that used this experimental scabies model is available in Table 8.1.

8.5 Optimisation of the Pig Model to Allow Therapeutic Trial of New Acaricides

The experimental pig model developed in Australia was successfully transferred into the premises of the Centre de Recherche BioMédicale (CRBM) at the veterinary college of Alfort (EnvA), France in 2014. To establish the first cohort, mites (*S. scabiei* var. *suis*) from naturally-infected pigs were used. Multiple visits to pig farms and slaughterhouses were necessary to source a large amount of living mites. Crusts heavily loaded with mites from three infected pigs found in a pig farm in Saint-Allouestre, Finistère, Brittany, France (Dominique Dreau) were sent to the

laboratory at CRBM on the day of the infection procedure. Three-week-old large white breed, specific pathogen-free (EOPS) siblings pigs from the same pig breeding facility (78,950 Gambais, Christian Lebeau) were housed at CRBM. Piglets were adjusted to standard stable and feed conditions for 2 weeks prior to the infection. Pre-treatment with dexamethasone (daily oral dosage at 0.2 mg/kg) in naive piglets, starting 1 week prior to infection was used to promote initial infection and exacerbate the disease. The delivery method of dexamethasone was oral tablets offered in marshmallows because of pig desire for sweetness. After 2 weeks of adaptation to their new housing and preparation with steroids, the infection was possible by directly introducing mite-infected skin crusts deep into the ear canal of the piglets, using the same technic as previously described by Mounsey et al. [25]. Crusts were dissected into small pieces (approximately 0.5 cm^2) containing between 600 and 800 mites. The animals were temporarily put under mild sedation to prevent dislodgement of the crusts by agitation and ensured successful infection. The first cutaneous lesion was visible 2 weeks after the infection and crusts appeared in all pigs 4 weeks post-infection. The ears were the first localisation to develop lesions, and within 4 weeks lesions spread gradually to the entire body.

To allow infection assessment, we designed a clinical score based on the skin surface affected by scabies lesions (scored 0–6: 0, 0%; 1, <10%; 2, 10%–29%; 3, 30%–49%; 4, 50%–69%; 5, 70%–89%; 6, 90%–100%), skin erythema intensity (scored 0–4: 0, no erythema; 1, mild; 2, moderate; 3, severe; 4, extremely severe) and crusting intensity (scored 2× 0–4: 0, no crust; 1, grey to white, thin and irregular 1–2 mm crust; 2, 3–5 mm crust; 3 = grey-brown >5 mm crust; and 4, >5 mm, hard crust from 0 to 6). The score is calculated for 5 different anatomic sites (ears, legs, tail, back and head) and added [32, 33]. To assess pruritus, we designed specific scoring system, based on the number of episodes of rubbing, scratching that can be recorded over 15 min. Flapping of the eras, rubbing against somethings and scratching ears with a hind leg were considered pruritus [32, 33].With these optimisations, the experimental pig model demonstrated its usefulness for preclinical assessment of drug candidates for the treatment of scabies [32, 33]. As a limitation of the model was the direct inoculation procedure that needs light sedation of pigs and is time consuming for a high number of pigs (around 12 to 15 pigs needed for a standard therapeutic trial), we tried a modification of the protocol with a direct skin-to-skin contact between infected pigs and naive piglets. Healthy piglets were placed in continuous contact for several weeks in the same pen with two other pigs that were already infected (same gender, all females). To enhance skin immunomodulation, a daily application of topical corticosteroids was started 4 weeks after the contact, added to the oral dexamethasone daily dose of 0.2 mg/kg and maintained for 2 weeks. Healthy pigs received hydrocortisone aceponate, a low potency (class I) topical corticosteroid, as a spray (Cortavance®, Virbac, Carros, France) and adult already infected pigs received clobetasol propionate, a very potent topical corticosteroids (class IV), in cream form (Clarelux®, Pierre Fabre, Paris, France) [55]. This procedure is less stressful for the pigs and is supposed to mimic a natural infection which takes place via a much smaller inoculum than that used in the initial cohorts. One of the consequences of the skin-to-skin direct infection is that the increase in

clinical scores is slow and a plateau is reached up to 11 weeks after the first contacts (versus 7 weeks when pigs are contaminated with a unique and large inoculum [32]). Furthermore, pigs seemed to develop a less homogeneous infection with groups that showed differences in terms of the number of mites [55].

Another optimisation that was made was to provide insight for projection and comparison of pig with human pharmacokinetics. Dosages of the drugs (e.g. ivermectin, moxidectin, afoxolaner) were feasible in plasma, but also in skin biopsies [32, 33]. Non-invasive tools are being developed to be able to dose the drugs in more detailed compartment of the skin such as the *stratum corneum*, or the sebum [56].

The list of published research projects that used this pig model is available in Table 8.1.

8.6 Conclusions

Animal models in scabies are being used to assess the biology of the mite, the host-interaction response, the quality and quantity of the immune response, to identify the optimal dose and formulation of a new drug, to determine its effectiveness and to evaluate the safety and toxicity of the drug formulation. Animal models help to make the translation from basic research to clinical application. Choosing an appropriate animal model has become increasingly important for the field, as each model has its own advantages and disadvantages. Thus, selecting the most appropriate animal model for the specific needs of the research project is critical. The criteria for selecting the right animal model and their characteristics have been presented in this review. Even if the porcine model is the most expensive and remains difficult to handle, it seems to be the most appropriate for scabies research for the moment. In the perspectives of reducing the use of experimental animals in research, focus should be done in the long term to use surrogate models, in vitro/ex vivo models or artificial models.

8.7 Supplemental Information

To maintain the porcine models, all animals are handled in accordance with guidelines established by the Australian, French and European regulations for care and use of animals for scientific purposes. In Australia, animals are handled in accordance with good animal practice as defined by the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and the NHMRC's Animal Code of Practice, and all animal work was conducted with ethical approval from the Queensland Animal Science Precinct (QASP), University of Queensland and QIMR Animal Ethics committees. In France, animals are maintained following Articles R. 214–87 to 214–137 du Code Rural et de la Pêche Maritime, Décret 2013–118 and the European Directive 2010/63/UE. The French animal model was approved by the Institutional Animal Care and Use Committee, Comitéd'éthique pour l'expérimentation animale and Anses/EnvA/Université Paris-Est Créteil, France (Approval no: 02515.03).

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Part III

Epidemiology and Burden of Scabies: Public Health Issues

Scabies: Epidemiology and Risk Factors

9

Emily Rudd and Claire Fuller

9.1 Worldwide Distribution of Scabies

Scabies is one of the most common dermatological conditions, particularly in low and middle income countries. Its worldwide prevalence was estimated to be 200 million by The Global Burden of Disease Study 2015 [1]. The disease affects people of all races and social classes.

Over the past century, scabies has become less prevalent in temperate regions and more common in tropical humid regions [1]. Countries of the Pacific have the highest prevalence, in particular Papua New Guinea (71%) and Fiji (32%). Panama, parts of Brazil and indigenous communities of northern Australia also have a high prevalence [2]. European and Middle Eastern countries demonstrate the lowest prevalence (<2.2%), albeit data are limited. There is no population-based data available from North America, most countries of Europe and non-Aboriginal populations of Australia [2].

Scabies is responsible for significant global health burden, particularly in vulnerable populations who often have limited access to health care. According to an analysis of the Global Burden of Disease study, scabies caused 0.21% of disability-adjusted life years (DALYs) from all conditions studied globally [1]. Scabies was ranked 101 of 246 conditions studied, just behind adverse drug reactions and viral skin disease. The analysis used prevalence estimates, which were weighted for disability, to calculate DALYs. Disability included skin disfigurement, skin pain and itch. Indirect morbidity, such as secondary bacterial infection, psychosocial and economic sequelae were not accounted for.

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In regions with the greatest scabies burden, namely East and Southeast Asia, the DALY burden of disease is greatest among children, adolescents and elderly people. This difference is much less pronounced in the low-burden regions of Northern America and Western Europe, where scabies prevalence is more evenly distributed across all age groups [1].

Overall, the incidence of scabies appears to be greater during the cooler seasons. It has been hypothesised that increased person-to-person contact and overcrowding in colder weather facilitate its spread [3, 4]. In addition, scabies mites are known to have improved survival in cooler conditions [5]. This was reported in a Taiwanese 14-year nationwide population-based study where the incidence of scabies was inversely correlated with high temperature and low humidity [6].

Previous studies indicated that scabies epidemics follow a cyclical course, occurring at 15- to 17-year intervals. This was thought to be a result of acquired immunity after infection [7]. However, this does not explain why, in endemic countries, scabies epidemics have been observed to persist [8]. It is more likely that fluctuations in prevalence are multi-factorial: a result of social and environmental changes such as war, climate and overcrowding [9, 10].

Crusted scabies is a highly contagious form of the disease which generally occurs among immunocompromised individuals affected by HIV, human T-cell leukaemia/lymphoma virus type 1 (HTLV-1), organ transplant recipients, institutionalised elderly or debilitated individuals [11]. There are an estimated two million scabies mites per patient with crusted scabies compared to approximately 10–15 mites per patient in classical scabies [12]. Patients with crusted scabies therefore act as core transmitters and potential sources of re-infection during intervention programmes [8].

9.2 High Income Country Settings

Most epidemiological data in the developed world are from hospital and clinic records with sparse data available on the prevalence of the disease in the general population.

In high-income countries, scabies commonly occurs sporadically (in individuals) or occasionally as outbreaks in institutional settings such as long-term care facilities, prisons, hospitals and orphanages. Epidemics may occur such as that potentially emerging in German speaking countries [13]. More commonly amongst children, migrants, the immunosuppressed and just possibly acaricide resistance.

There seems to be an even distribution of scabies burden between men and women in most world regions [1]. This is in contrast to United Kingdom where a female predominance has been observed [7]. A retrospective review of a UK general practice database (1997–2005) calculated that the mean prevalence of scabies was 2.81 per 1000 in females and 2.27 per 1000 in males [3]. It has been suggested that women are more willing to consult their GP than men, which might account for this difference.

There is variation in the prevalence of scabies between age groups within high income countries, although this difference is less marked than in developing countries. Lassa's review showed that, in the United Kingdom, the highest prevalence of scabies was in the 10–19-year age group [7]. The prevalence dropped steadily from the 20–29-age group to the 70–79-age group and then increased in the 80+ year age group. Many studies have shown an increased prevalence in the pre-school and school age groups [3, 10]. This is thought to be due to increased socialisation within these groups.

Immunocompromised, old age and institutionalisation increase the risk of scabies infestation [3]. A study in Northern Taiwan found that elderly institutionalised patients with certain risk factors had higher rates of scabies infection. These included being bedridden, living in a nursing home, poor clinical status on admission and long-term use of a catheter [14]. It is notable that the clinical presentation of scabies in the elderly population often differs from the classic presentation. A prospective observational study in southeast England showed that 51% of care home residents, who were diagnosed with scabies, were asymptomatic. Moreover, clinical signs were often subtle and concentrated in areas normally covered by clothing. This is likely to contribute to diagnostic delay and suboptimal management. A dementia diagnosis was also predictive of scabies; perhaps wandering behaviours and an increased number of physical contacts could increase transmission. A high index of suspicion and careful examination is required in this vulnerable patient group [15].

Institutional scabies is associated with significant morbidity, work burden and economic burden [11]. The economic burden encompasses medication costs, labour expenses, costs of prolonged hospital stay and ward closures [16]. This can be appreciated in a French study that described an outbreak in a French teaching hospital affecting 51 staff and patients, 7 of whom had recurrent attacks. Mass treatment was administered, and it took 3 months to successfully eradicate the infection [17].

9.3 Tropical and Resource-Poor Settings

Scabies most commonly occurs as epidemics in high-income countries, whereas the disease is often endemic in many tropical, resource-poor communities [18]. Low-income countries have the highest rates of scabies infection with considerable morbidity. In particular, island countries of the Pacific, Panama and parts of Brazil. Indigenous communities of Northern Australia are also significantly affected. Poverty is associated with a multitude of risk factors for scabies infection including inadequate living conditions, limited access to water, overcrowding, malnutrition and low levels of education. Limited access to healthcare also delays the diagnosis and treatment of scabies [19].

Lower ambient temperatures and higher relative humidity are associated with prolonged off-host survival of the scabies mite. However, the importance of mites and fomites in endemic settings needs to be clarified [18]. Overcrowding is an important epidemiological predictor for scabies. For example, a Brazilian study

showed that scabies was twice as prevalent in a densely populated urban slum than in a fishing community where families lived in larger spaces [19].

Natural disasters amplify the aforementioned risk factors such as poor access to water, malnutrition and overcrowding and are therefore associated with infectious disease outbreaks. A recent example of this was the scabies outbreak in Ethiopia following the El-Nino drought in 2015–2016 [20].

In endemic communities, the infestations are generally more severe; there is increased morbidity and chronic sequelae such as acute post-streptococcal glomerulonephritis and rheumatic fever [19]. The reasons for this are multifactorial including poor nutritional status, poor access to healthcare systems, inaccurate diagnosis and subsequent re-infestation [19]. The paediatric group, in whom scabies is more prevalent, are also particularly susceptible to the more severe manifestations of scabies and subsequent complications.

A study of 105 patients with scabies living in an urban Brazilian slum has demonstrated the considerable impact of the disease on quality of life, which increased in parallel to the degree of itching and severity of disease. Approximately 80% patients stated that their quality of life was affected by scabies; 13.9% patients reported severe restrictions (using a modified Dermatology Life Quality Index). Shame, embarrassment, social exclusion and stigmatisation were most frequently perceived, with more impact on the female sex [21]. In addition to the psychosocial impact, there is a significant economic burden in low-income communities; affected families often spend a significant proportion of household income on treatment [5]. Further research is needed to assess the true extent of the socio-economic burden worldwide.

9.4 Future Work on Disease Control

In conclusion, scabies is a worldwide public health issue that disproportionally affects disadvantaged populations. The disease has potentially devastating physical manifestations, and furthermore, the social, economic and psychological sequelae can be substantial. The recognition of scabies as a neglected tropical disease by the World Health Wwwddxscc xx see sedewe Organization in 2018 has put scabies on the global health agenda, moving closer to the ultimate aim of global disease control.

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Public Health Issues, Scabies Surveillance and Awareness

10

Roderick Hay

The impact of scabies on the health of the public is variable, both between and within countries. In some areas, the sheer volume of cases means that scabies dominates the pattern of skin disease seen at front line level. In such situations, the impact of this case load and the high rate of transmission in the community create a public health problem that demands action. The further impact of secondary streptococcal infection and the consequent potential for acute and chronic renal damage or rheumatic fever makes the case for community interventions even stronger. Yet, even in those areas where scabies occurs at a low prevalence, the effect of the infection in specific community settings such as care homes for older persons can give rise to major local challenges to public health, simply because of the deleterious effects of the infection on a closed community and the potential for continuing transmission, providing a valid reason for an effective intervention within that institution. Again, while the longer-term consequences of scabies are discussed in subsequent chapters, the effect of scabies on other disease states such as renal failure, heart disease and infant mortality through septicaemia is unknown in these closed community settings.

While all disease could ultimately be thought of as a problem of public health, the judgement as to whether to intervene as a community initiative is largely determined by the circumstances, and usually, this is assessed on a case-by-case basis. The factors that make it more likely for a single disease to be regarded as a public health concern include high prevalence and the risk of wider spread, the involvement of the vulnerable such as the very young or very old or families, the risk that it may produce significant morbidity in addition to mortality, the secondary effects on mental health and social welfare and its cost both to the state as well as the individual. A further element in justifying intervention is the feasibility and cost of deploying effective treatment to control the outbreak and prevent spread. Often once

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an infection, for instance, cannot be controlled by measures normally satisfactory at individual treatment level, it becomes a public health problem. What do we know about scabies in this context?

The prevalence of scabies has been fully discussed in the previous chapter. It has been seen that in many industrial countries the prevalence rate is low and the disease treatable on an individual basis. The case for wide-scale public health intervention is comparatively weak in these settings. Some of the subsequent chapters document large-scale interventions in community settings that are largely driven by the sheer scale of the infection such as in villages in Fiji or the involvement of vulnerable communities such as those affected by drought in Ethiopia. Both of these initiatives have been backed as public health measures by strong governmental support. However, there are also outbreaks in specific communities where scabies is difficult to contain and where, of necessity, it places a call on local public health resources. Three examples are elderly care homes, schools (particularly residential schools) and prisons. The continuing displacement of populations or refugees through warfare, civil disturbance and persecution as well as natural disasters into overcrowded and under-resourced accommodation is a further source of local outbreaks of scabies that require community-wide interventions.

10.1 Institutional Scabies

10.1.1 Residential Care Homes

Scabies is an important and well-recognised problem when it causes outbreaks in elderly care homes. These are usually residential and designed for the care of a small, but frail, population of residents, together with their carers and health care workers. These outbreaks are often extensive, potentially affecting the majority of the residential patients and staff [1, 2]. The reasons for the high infection rate and spread are various, but generally scabies in the elderly presents in an atypical manner and may not be recognised until the disease has taken a firm grip [3, 4]. There may be less itching, and lesions may be clustered in an unusual distribution—such as under-pressure areas in immobile patients. Some patients may also not have other characteristic signs of scabies leading to failure of recognition and delayed treatment. Dementia is a significant risk factor [4]. In a study of a US care home where there had been a 5-month-long outbreak of scabies, all infected residents showed lesions that mainly affected the trunk [3]. Twelve of them had diffuse erythematous or papulosquamous lesions, without noticeable burrows, and itching was only reported by five of those affected. The investigators also noted a poor response rate to topical permethrin in those with cognitive impairment (dementia) suggesting other reasons for atypical behaviour. They recommended the bold step that the diagnosis of scabies should be considered in any nursing home resident with an unexplained generalised rash. A further obstacle to early recognition is unfamiliarity with the disease amongst care home staff and even the visiting medical staff who are contracted to provide medical support.

In addition, the prevalence of scabies and, as a consequence, load of scabies mites may be higher than in a younger and healthier population. For instance, in survey of the homes of infected patients and five care homes where infection had been confirmed, dust samples from 44% of infested patients' homes were found to contain scabies mites, and in 64% of these samples, they were judged to be viable. They were found on floors and chairs or sofas [5]. They were fewer in number from the surfaces of care homes. The investigators speculated that mite-contaminated fomites may be less important in the transmission of scabies in nursing homes than in private homes but that it could occur in either setting. This is a recipe for rapid spread within a closed community. In support of this, a more recent study of 7 care homes in the United Kingdom showed attack rates that ranged from 2% to 50% in inhabitants [4]. Similar high infection rates have been reported from other countries from Germany to Brazil in elderly care institutions. In the latter study over a 7-year period, the incidence of scabies varied from 21% to 63% in those institutions surveyed [6]. Notwithstanding its importance in residential homes, the presence of scabies in somewhat higher levels than normal has also been reported in older persons in outpatient settings [7]. Even in areas where childhood infection dominates the pattern of scabies, a rise in the incidence of this infection in older persons has been reported, e.g., Fiji [8]. So age and frailty may also predispose to an increased risk of infection due to increased susceptibility.

Crusted scabies may be seen in the elderly which is a further reason for high transmission rates, compounded by the problem referred to previously of the shedding of viable mites and the overall susceptibility of the population. The result is the infection of many individuals within a single residential institution and the need for concerted treatment and surveillance, often involving health care workers from outside the immediate setting of the home. This implies the deployment of additional resources, and it constitutes a public health problem, albeit in a local setting.

10.1.2 Schools

The presence of scabies in residential schools follows a similar pattern, although here overcrowding in living quarters and close living conditions, rather than innate susceptibility, play a key role in spread amongst pupils [9, 10]. In many areas where there is poverty and household overcrowding, there is a high prevalence rate of infection by scabies amongst school age children attending regular days schools [11, 12]. However, where children are living in residential schools, this risk of cross infestation rises irrespective of the background level of infection in the community. Outbreaks of scabies have been reported from residential schools in different settings from the United Kingdom to Bangladesh. In the latter example, the authors describe the deployment of a concerted public health control programme for both children and teachers using topically applied permethrin, providing instruction in personal hygiene and health care and prevention and interrupting control by reducing contamination—storage of clothing, laundry. This reduced the prevalence in

residential schools of infection from 61% to 5%, whereas in a control school population during this period, infection rate only declined from 62% to 50% [10].

10.1.3 Prisons

Scabies in prisons has mainly been recorded in tropical areas as well as in those prisons where there is endemic overcrowding which favours spread [13, 14]. While the conditions in goals is beyond the scope of this chapter, in facilities where overcrowding is both the norm and no attempt has been made to provide adequate accommodation, scabies can be an inevitable consequence of the introduction of a single infected prisoner that results in rapid spread and wide dissemination of the disease to others. As with residential homes, the arrival of a single patient with crusted scabies can lead to a massive outbreak. The situation is also worsened in goals where HIV infection is prominent [15]. Outbreaks of scabies in prisons have been reported in many countries. Mass treatment with ivermectin has been advocated in such cases [16, 17].

10.1.4 Refugee Camps

A similar situation can occur in populations displaced by war or natural disaster, refugees who are often housed in poor accommodation where overcrowding even amongst families is so often the case. Here again the introduction of a single individual with scabies can result in spread. In a study of children displaced by war into temporary camps in Sierra Leone, the prevalence of scabies in a study population of 125 children between the ages of 1 and 15 was age dependent, with 77% of children under 5 years being affected increasing to 86% of 5- to 9-year-olds [18]. In a more recent example in Ethiopia where drought had displaced large populations into overcrowded facilities, an estimated 373,000 people in Amhara state were affected by a massive scabies outbreak [19].

10.2 The Burden and Impact of Scabies

10.2.1 Quality of Life and Disability

The medical impact of scabies in populations can be assessed by different quantifiable measures such as the DALY score. Figures taken for the current Global Burden of Disease study illustrate this well. The overall DALY scores of scabies in areas where it has a high prevalence are relatively high, as although the mortality rate is low, the sheer numbers of cases lead to increased DALYs. In this assessment, disability has been calculated on the basis of symptoms such as itch and disfigurement directly attributable to involvement of the skin—secondary consequences such as renal damage are reported under nephritis (of all causes) [20]. In an analysis of the

2015 GBD, scabies was found to be responsible for 0.21% of DALYs from all conditions studied worldwide. These ranged from east Asia (age-standardised DALYs 136.32), to Oceania (120.34) and tropical Latin America (99.94). Five countries with the greatest scabies burden were Indonesia (age-standardised DALYs 153.86), China (138.25), Timor-Leste (136.67), Vanuatu (131.59) and Fiji (130.91). The highest DALY burdens were in children, adolescents and the elderly.

The above studies used an objective measure of disability that discounts the interpretation and attitudes and thoughts of patients, but scabies has a major subjective impact on health and well-being which takes these more personal aspects of the impact of disease into consideration. Here, Quality of Life measures play a greater role. Using a meta-analysis of studies that had employed the Children's Dermatology Quality of Life Index to assess the impact of different childhood skin conditions on well-being [21], the authors found that scabies had one of the highest impact scores at 9.2 (0.0–20.3), atopic eczema scored a mean of 8.5 (7.1–9.8) and psoriasis 8.0 (3.9–12.1). The study had limitations in that it only included two studies of scabies in childhood; but potentially the impact of Quality of Life is huge, and it showed that was equal to, or greater than, the two other skin diseases seen in children (psoriasis and eczema) thought by conventional wisdom to have the greatest impact on life quality.

A detailed study of quality of life of patients with scabies in an urban slum in Fortaleza, Brazil, investigated 58 children and 57 adults [22]. The main items that illustrate quality impairment were identified as feelings of shame (adults 77.2% and children 46.6%), the need to dress differently (35.1% vs. 29.3%), social exclusion (24.6% vs. 17.9%) and stigmatisation (21.1% vs. 25.0%). Twenty-six percent of children reported teasing.

10.2.2 Economic Impact

In addition, scabies may have a profound economic impact on poor communities. This was highlighted by work in the Northern territory of Australia where in local communities the cost of individual treatment coupled with investigations and misdiagnosis meant that the disease posed a considerable cash burden on individuals and health providers [23]. In a study carried out in Mexico, it was found that, on average, families were spending 34$ (US) over 3 months on treatment, which had not worked, to manage scabies [24]. In this area, the local economy is based on a mixed model with barter and exchange of goods and services mixed with a cash economy. In this situation, this cash sum rapidly exhausts household cash reserves which would be better spent on additional food or effective medications.

This economic cost extends into other community settings. For instance, in residential care facilities, outbreaks can result in a significant burden of additional resources including medications, external health workers and laundry. In a review carried out that focused on the patterns seen in institutional outbreaks, it was found that, on average, scabies outbreaks lasted for 3 months, with a median attack rate of 38%, all accounting for additional work and personnel. There has also, in the past 10 years, been a shift from the use of the older and cheaper medications such as

benzyl benzoate, and in one study, the recent trend was to use 5% permethrin and oral ivermectin [25]. Scabies had been misdiagnosed in 43% of these outbreaks, meaning delay in obtaining appropriate effective medications and further medical consultations. As an illustration, an outbreak of scabies in a Canadian long-term care facility with two index cases, one with classic scabies and the other crusted scabies, resulted in significant additional costs [26]. The total cost involved in controlling the outbreak came to a total of $200,000 (CDN); there was also a further potential cost through loss of business through adverse publicity.

10.3 Solutions

A reasonable conclusion from these studies is that there is a key need to raise awareness of scabies and its impact on health and well-being. Yet, scabies often remains poorly taught in health training programmes and therefore under- or mis-diagnosed. The study in Mexico referred to previously had a significant impact within a cash-poor economic setting simply because of the high rate of ineffective treatment due to a low level of understanding of the disease and its management. Programmes designed to address this learning gap have been used in different parts of the world [27]. For instance, a community-based programme for instruction of front-line health workers using an algorithm to determine treatment pathways carried out throughout Mali showed that it was possible with short focussed sessions to improve the knowledge and skills of this cadre of health staff to recognise and treat four common skin diseases, scabies being one of them [28]. Further training programmes at primary care level targeting scabies amongst other skin conditions have been developed in Mexico [29]. These are but a few of several initiatives to improve the care of those with scabies [30, 31]. Reducing the knowledge and information gap along with effective interventions is key to success in managing scabies in communities.

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Scabies and Secondary Infections

11

Shu Ki Tsoi, Li Jun Thean, Andrew C. Steer, and Daniel Engelman

11.1 Introduction

In addition to the direct morbidity caused by scabies infestation, including itch and skin lesions, scabies causes morbidity by increasing host susceptibility to secondary bacterial skin infection, most commonly impetigo. The most common pathogens that cause impetigo are *Streptococcus pyogenes* (group A Streptococcus, GAS) and *Staphylococcus aureus*. Impetigo can develop into complicated skin and soft tissue and invasive infections including toxic shock syndrome. In addition, GAS skin infection can trigger immune-mediated sequelae such as post-streptococcal glomerulonephritis and possibly also acute rheumatic fever [1–3]. The causal relationship between scabies and bacterial infection has been described through clinical and

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epidemiological associations and laboratory-based studies of the mite and host. However, the proportion of these infections attributable to scabies has varied across studies and regions, and the reasons for this apparent variation are yet to be defined. In this chapter, we review the secondary bacterial infections that may arise due to scabies. Post-infectious complications are discussed in Chap. 13.

11.2 Impetigo

Impetigo (also referred to as 'school sores') is a common, superficial skin infection [4]. There is a high prevalence of impetigo in tropical and low-middle-income settings, with an estimated global point prevalence of 162 million, and children are most commonly affected [5]. The causal relationship between scabies and impetigo has been established through observational epidemiological studies with an attributable risk estimated between 41% and 93% [6–8] in settings where scabies is endemic [5]. Intervention trials have demonstrated that impetigo prevalence declines following public health interventions aimed at the control of scabies [7, 9].

11.2.1 Predisposition to Impetigo Due to Scabies

There are several mechanisms by which scabies predisposes to impetigo. First, scabies causes intense itch and subsequent scratching. This direct trauma causes breaches in the skin barrier, enabling bacteria to penetrate the epidermis. Second, scabies mites secrete serine protease inhibitors which inhibit the host's innate immune response, thus promoting bacterial survival and proliferation. Currently, 33 scabies mite-inactive serine proteases and six scabies mite serpins have been identified, all of which downregulate the complement system to some extent [10, 11]. These inhibitors have been identified in the mite gut and epidermal burrows, creating an ideal microenvironment for bacterial proliferation [12]. Specifically, the scabies mite serpin B4 (SMSB4) promotes growth of GAS *in vitro* by inhibiting opsonophagocytosis, reducing formation of C3 convertase and preventing activation of the complement cascade [13]. Reduction in the formation of anaphylatoxin C5a and C3b deposition prevents recruitment of white blood cells to the site of infection and subsequent phagocytosis of microbes [13]. SMSB4 has also been shown to disrupt phagocytosis of *S. aureus* by neutrophils [14]. *In vivo* models using pigs infected with the scabies mite have shown an increase in *Staphylococcus* spp. in the porcine skin compared to those not infected with scabies [15]. These studies further strengthen the epidemiological links between scabies and impetigo infection.

11.2.2 Clinical Presentation

Impetigo presents as bullous or papular lesions, which can progress to honey-coloured, crusted papules and ulcers. Impetigo is commonly found on exposed body parts such as the arms, legs and face. Impetigo is not usually associated with

fever or systemic symptoms [16]. Similarly, impetiginised scabies lesions are characterised by honey-coloured crusts overlying the pustules and papules. The diagnosis of impetigo is made clinically, and can be supported with clinical guidelines such as the WHO Integrated Management of Childhood Illness (IMCI) algorithm [17]. In cases that do not respond to recommended treatment, skin swabs can be taken for Gram staining, bacterial culture and antibiotic susceptibility testing. These laboratory resources may not be readily available in many remote or low-income settings.

11.2.3 Epidemiology of Scabies and Impetigo

A number of studies conducted in tropical developing countries, predominantly across Oceania, have explored the epidemiologic link between scabies and impetigo, with the majority reporting an increased risk of impetigo associated with scabies infestation (Table 11.1). In a systematic review of global scabies and impetigo prevalence published in 2015, a strong correlation was not identified between the two [5].

11.2.3.1 Oceania

There have been several large-scale surveys of scabies and impetigo in Pacific Island countries. These studies have consistently found an association between impetigo and scabies, although the strength of this association has varied. In the Solomon Islands, individuals were 1.5 to 2.5 times more likely to have impetigo if they had scabies [8, 25]. In Fiji, a trial found 62.5% of cases with severe scabies had concomitant impetigo [20]. Participants had a 2.6 times greater risk of impetigo if they had scabies. In addition, scabies was shown to contribute to a substantial burden of impetigo disease, with 33.6% of impetigo cases attributed to scabies. A Fijian national survey found a prevalence of scabies and impetigo of 23.6% and 19.6% respectively, with a population attributable risk of impetigo due to scabies of 93% [6]. This is much higher than in previous studies and may partly be due to a high proportion of school-aged participants. A separate study from Fiji identified the odds ratio of a child having active impetigo if scabies was present as 2.4 (95% CI 1.6–3.7) [18].

Some of the highest prevalences of scabies have been described in remote Indigenous communities in Australia, with a median prevalence of up to 45% among children. A self-controlled case series in the Northern Territory of Australia found that patients with scabies were almost 12 times more likely to develop impetigo, although the magnitude of this association was lower in infants [21]. The Skin Sore Trial in the Northern Territory involved over 500 children and found an odds of 1.9 greater risk of impetigo among those with scabies [19].

11.2.3.2 Asia

In Asia, there are limited data in middle-high economic countries. One study conducted in rural areas of Nepal found an estimated scabies prevalence of 3.4%, with impetigo presenting relatively infrequently at 1.6%. However, bacterial skin and soft tissue infections were noted to be very common in patients presenting to

Table 11.1 Studies of scabies and impetigo and prevalence since 2006, ordered by date of study

Study	Year	Country	Number of participants	Scabies prevalence	Impetigo prevalence	Association
Steer [18]	2006–2007	Fiji	3462 school age children	36.4% (34.8–38.0)	18.5% (17.2–19.8)	OR 2.4 (1.6–3.7)
Romani [6]	2015	Fiji	10,887	23.6% (18.5% adjusted)	19.6%	Population AR 93%
Romani [5]	2015	Global (Systematic review)	48 studies	0.2%–71.4% (most >10% except Europe and Middle East)	16%–52%	N/A
Mason [8]	2016	Solomon Islands	1908	19.2% (17.5–21.0)	32.7% (30.6–34.8)	AOR 2.0 (1.6–2.6)
Tasani [19]	2016	Northern Territory, Australia	508 (1715)	14.1%		OR 1.9 (1.4–2.6)
Romani [20]	2017	Fiji	2051	36.4% (34.3–38.5)	23.4% (21.5–25.2)	Population AR 36.3%
Aung [21]	2018	Northern Territory, Australia	291 (417)		75%	IRR 11.9 (10.3–13.7)
Korte [22]	2018	Timor-Leste	1396	22.4% (20.2–24.7)	9.7% (8.3–11.4)	RR 2.5 aOR 4.4 (2.9–6.8)
Armitage [23]	2019	Gambia	1441	15.9% (12.2–20.4)	17.4% (10.4–27.7)	aOR 2.74 (1.61–4.67)
Marks [24]	2019	Bijagos Archipelago, Guinea Bissau	1062	5.2% (4.0–6.8)	7.7% (6.2–9.5)	aOR 3.1
Osti [25]	2019	Solomon Islands	324	54.3% (48.7–59.8)	32.1% (27.0–37.5)	ARR 1.5 (1.1–2) Population attributable risk 11.8% (1.7–21.7)
Davidson [26]	2020	Australia in Aboriginal Australians	Narrative Review	16.1%–35.0%	45% (34–49)	

dermatological clinics [27]. There is a high prevalence of infectious skin conditions in India. A study in a rural community of India estimated prevalence of scabies of 13.5%, with approximately 10% observed to have impetigo or pyoderma [28]. A lower prevalence of scabies was observed in mountainous regions (4.4%) which

could be explained by the cooler climate [29]. In Timor-Leste, a study of school students found a prevalence of scabies of 22.4% with almost half of these students co-infected with impetigo. Students were 2.5 times more likely to have impetigo if they had scabies infection [22].

11.2.3.3 Africa

Skin infections including scabies and impetigo are common in Africa. A number of household surveys in Tanzania estimated scabies prevalence to be between 4% [30] and 6% [31]. In one village population, investigators reported most scabies cases appeared to have secondary bacterial infections (proportion not provided) [31]. In rural areas in northern Egypt, relatively low prevalence of scabies (1.7%) and impetigo (3.31%) was identified. It was unclear why these skin infections were relatively uncommon in this study. However, other studies from Egypt identified higher prevalence of scabies (5%–24%) [32, 33]. Similarly, the prevalence of impetigo has been reported as high as 10% in other rural regions of Egypt [33]. Further south in Mbam, Cameroon, there was a lower prevalence of scabies (2.82%) identified in a survey of rural areas. Impetigo prevalence was estimated at 5.24% [34]. One possible explanation for the relatively low prevalence of scabies and higher prevalence of impetigo is that there are parasitic infections such as onchocerciasis in the region that can also progress secondary bacterial infections. In the Bijagos Archipelago, off the coast of Guinea-Bissau, an adjusted odds ratio of 3.0 was found between scabies and impetigo in those less than 10 years old [24]. Similarly in The Gambia, a study involving participants younger than 5 years old found an adjusted odds ratio of 2.74 [23].

11.2.3.4 Middle East

A household survey in Basrah, Iraq, found an estimated prevalence of scabies and impetigo of 0.5% and 0.9%, respectively, with a greater number of cases in overcrowded lower socio-economic areas [35]. A larger study in Iraq involving two governorates found a higher prevalence of both scabies and impetigo at 1.9% and 6.7%, respectively, and also identified higher prevalence of skin infections in low socioeconomic groups (39.6% vs. 20.3%) [36].

11.2.3.5 Latin America

In resource-limited areas of Brazil, scabies prevalence ranges from 9% to 10% [37–39], with 35% to 38% of cases also having impetigo [37, 39]. The prevalence of scabies was found to be lower in less crowded regions such as fishing communities (3.8%); however, the proportion of secondary bacterial infection was still high with 19% of scabies cases affected [38].

11.2.3.6 High-Income Countries

There are few epidemiological studies in the United States and Europe. In Portugal, the estimated prevalences of scabies and impetigo in impetigo have previously been reported as 1.2% and 0.7%, respectively [40].

11.2.4 Treatment

Treatment options for impetigo include topical, oral or intramuscular agents. A number of factors should be considered when deciding on treatment such as disease severity, likelihood of adherence to treatment, community prevalence and antimicrobial resistance.

According to a Cochrane systematic review, topical antibiotics such as mupirocin, fusidic acid and retapamulin were found to be the most effective treatment for uncomplicated impetigo (five lesions or fewer) [41]. However, topical use of mupirocin and fusidic acid is associated with rapid development of antimicrobial resistance in *S. aureus* [42]. Treatment guidelines for uncomplicated impetigo vary between countries. For example, in the United Kingdom, topical hydrogen peroxide cream is recommended for uncomplicated impetigo, with fusidic acid recommended as second-line [43]. In Australia and United States, topical mupirocin is recommended as first line [44, 45]. However, in Indigenous Australian communities, topical agents are not recommended due to concerns regarding resistance [46].

For moderate or extensive impetigo (more than five lesions), systemic antibiotics are recommended, with suggested empirical treatment to cover for *S. aureus*. The choice of antibiotics depends on the local risk of methicillin-resistant *S. aureus* (MRSA). Suitable oral agents for methicillin sensitive *S. aureus* include first generation cephalosporins (for example, cephalexin), anti-staphylococcal penicillins (flucloxacillin, cloxacillin or dicloxacillin) and trimethoprim-sulfamethoxazole [42]. In highly endemic, resource-limited settings, intramuscular benzathine penicillin G has also been used to treat impetigo [47, 48]. It may be most useful in settings where access to follow up is challenging or compliance to treatment is a concern. However, its effectiveness may be limited when *S. aureus* is the predominant pathogen [48]. Further, the intramuscular route is painful, therefore potentially limiting its acceptability [49].

In cases where MRSA infection is suspected, or in areas where there is a high risk of MRSA, oral lincosamides (clindamycin) or trimethoprim-sulfamethoxazole is recommended [50]. While effective against MRSA, clindamycin has an unpalatable taste, an important consideration when treating children. Trimethoprim-sulfamethoxazole is effective against MRSA, has some demonstrated *in vivo* and *in vitro* action against GAS, and is generally well tolerated [51, 52]. A randomised, controlled trial comparing the use of a short 3- to 5-day course of oral trimethoprim-sulfamethoxazole to intramuscular benzathine penicillin G in Indigenous Australian children demonstrated non-inferiority for the treatment of impetigo [48].

11.2.5 Prevention

Preventative strategies are important in the public health response to impetigo. In scabies-endemic settings, community-based interventions which have reduced scabies prevalence have also led to significant reductions in impetigo prevalence [53]. Ivermectin-based mass drug administration (MDA) for scabies control is a

promising strategy for the prevention of impetigo, with several trials reporting a consequential fall in impetigo prevalence following this intervention. Further information regarding MDA for scabies prevention is presented in Chap. 28.

In Fiji, the SHIFT trial demonstrated a 67% reduction in impetigo prevalence accompanying the 94% decline in scabies prevalence 12 months after a single round of ivermectin-based MDA. At 24 months follow up, impetigo prevalence had fallen by 90% (95% CI, 74–99) from baseline [54]. The AIM study in the Solomon Islands demonstrated that these results could be replicated on a larger scale (study population of 26,372). In this study, co-administration of ivermectin and azithromycin through MDA led to a fall in impetigo prevalence from 24.8% at baseline to 6.4%, 12 months after MDA. Although there was a rebound to 9.6% at 36 months after the intervention, this still represents a 61% relative reduction in prevalence after a single round in MDA [55]. This study also showed a 51% reduction in attendance to healthcare clinics for skin sores, boils and abscesses 3 months following MDA [56]. The addition of azithromycin was not shown to produce any additional benefit in impetigo prevalence. A subsequent community randomised trial of MDA for scabies/impetigo using ivermectin and azithromycin versus ivermectin alone in the Solomon Islands found no difference in the reduction in impetigo prevalence between the two groups (relative reduction of 72.7%, 95% CI 8.9–96.5, in the ivermectin and azithromycin group versus 75.2%, 95% CI 67.9–100, in the ivermectin-only group, $p = 0.49$) [57]. There was a transient rise in macrolide-resistant *S. aureus* strains among those with impetigo in the ivermectin and azithromycin group, but this returned to baseline by 12 months.

11.3 Complicated Skin and Soft Tissue Infections

Impetigo may progress to deeper or complicated skin and soft tissue infections (SSTI) including cellulitis, abscess, pyomyositis and necrotising fasciitis. These conditions present a substantial burden on affected individuals, their families and the health systems that care for them. Estimates of global morbidity and mortality due to skin diseases in 2017 based on the Global Burden of Disease Study 2013 demonstrated a high proportion of SSTI in Oceania and Africa caused by cellulitis and pyoderma [58].

While many health presentations for complicated SSTIs are managed in ambulatory care settings [59], a proportion experience more severe disease and require hospitalisation. There appears to be a higher incidence of hospital admissions among Indigenous populations, suggesting environmental and socioeconomic factors are relevant risk factors. For example, the annual incidence of SSTI admissions among Indigenous Australians is more than five times greater than non-Indigenous Australians (1890 compared to 290 per 100,000) [60]. In New Zealand the annual incidence of SSTI admissions among children aged less than 14 years was 20 times greater among Pacific Islanders (4685 compared to 229 per 100,000) and almost four times greater in the Maori population (886 per 100,000) than all other ethnicities [61]. There remains limited information regarding the epidemiology of complicated SSTIs in scabies-endemic settings.

Individuals with crusted scabies (see Chap. 17) have a very high risk of developing SSTI and severe bacterial infections. Most cases occur in individuals with comorbidities, particularly immunocompromised states, and there is significant mortality associated with secondary infection [62, 63].

11.4 Invasive Infections

Cutaneous infection with *S. aureus* and GAS can progress to invasive infection, defined as infection of a usually sterile body site. Clinical presentations include, but are not limited to: bacteraemia, septic arthritis, osteomyelitis, pleuro-pulmonary infections, meningitis and infective endocarditis. Invasive *S. aureus* and GAS infections result in high morbidity and mortality [64–66]. The burden of disease is disproportionately borne by low-middle-income countries [67]. Although only sparsely described, available data incidate a higher incidence of invasive *S. aureus* and GAS infections and case fatality in low-middle-income settings compared to high-income settings.

11.4.1 Invasive *Staphylococcus aureus* Infections

S. aureus is the most common cause of bacteraemia, osteoarticular infections, pleuropulmonary infections and infective endocarditis [16]. The annual incidence of invasive *S. aureus* infections in high-income countries ranges between 19.0 and 33.7 per 100,000 population [68, 69]. Less is known about all-age incidence in low-middle-income settings where scabies is endemic. A 2007 study in Fiji estimated the incidence of *S. aureus* bacteraemia at 50 per 100,000 population [70].

Established risk factors for invasive *S. aureus* infections include extremities of age, ethnicity, immunosuppression, intravenous drug use and haemodialysis [68, 69, 71]. Invasive *S. aureus* infections results in significant morbidity and mortality, with an estimated case fatality rate of 20% (30-day all-cause mortality) and 13% for infection-related fatality. This is equivalent to a mortality rate of 2 to 10 deaths per 100,000 population globally. Invasive *S. aureus* infections therefore cause more deaths than AIDS, tuberculosis and viral hepatitis combined. Despite this burden, the community impact of invasive *S. aureus* infections, especially in low-middle-income countries, remains poorly understood [71].

There have been a number of cases of *S. aureus* bacteraemia reported from Indigenous Australian populations secondary to scabies infection [72]. An investigation into a cluster of 54 cases of invasive *S. aureus* infections in the Northern Territory identified scabies and impetigo as the greatest risk factors, occurring in 31% of cases [73]. In Indigenous children in Australia, where impetigo is often secondary to scabies infection, invasive *S. aureus* infections has been found to occur more than ten times more frequently than in non-Indigenous children [74].

11.4.2 Invasive Group A Streptococcus

Invasive GAS infections are estimated to occur in 660,000 people and result in 163,000 deaths annually [67]. Low-middle-income settings have incidence rates several times higher compared to high-income settings [75]. Studies from high-income settings such as North America, urban Australia and Scandinavia describe annual invasive GAS infection incidence to be between 3.8 and 4.3 cases per 100,000 population. Available data from low-middle-income settings suggest a much higher incidence – for example, a study in Fiji in 2007 estimated the incidence to be 9.9 per 100,000 population [76]. Like invasive *S. aureus* infections, the highest incidence of invasive GAS infections is among the youngest and oldest age groups [64]. Additional risk factors for developing invasive GAS infections include pre-existing diseases such as diabetes, heart disease and malignancy, concurrent infections with influenza and varicella zoster viruses, household crowding, strain virulence, and impaired host immunity [26]. Case fatality rates range from 8% to 16% in high-income countries and are much higher in low-middle-income countries at 25% to 32%, comparable to invasive meningococcal disease [64, 76].

Several invasive infections can also occur in patients with crusted scabies. A number of case reports can be found describing bacteraemia caused by a range of organisms including *S. aureus, Citrobacter spp.* and *Pseudomonas aeruginosa* among patients with crusted scabies [62, 77–79]. Invasive diseases such as septic arthritis, pneumonia, pericarditis, central nervous system infections have all been reported as secondary bacterial complications of crusted scabies [80–82]. Crusted scabies carries a high mortality rate secondary to overwhelming sepsis as a result of underlying predisposing immunosuppression present in many patients [83].

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Morbidity of Scabies in Resource-Poor Communities

12

Jorg Heukelbach and Guadalupe E. Estrada Chávez

12.1 Introduction

Scabies is a Neglected Tropical Disease associated with poverty and sub-standard living conditions [1–3]. Risk factors commonly described include illiteracy, social attitudes, migration, limited access to health care services, crowding, poor housing conditions, poor hygienic conditions, and sharing of clothes and bed linen [1, 3–10]. In resource-poor communities, scabies is often endemic, as a result of under-recognition of the disease and limited access to an effective health system and specific treatment. As access to healthcare services is difficult for many at risk, inappropriate medication practices may complicate disease conditions [1, 11].

In these settings, frequencies may reach escalating values, as exemplified by remote rural communities in Nigeria (65%) [1] and Papua New Guinea (80%) [12]. In specific groups, extremely high prevalences have been observed all over the world, such as in African displacement camps (67%) [13], Thai orphanages (87%) [14], a Korean leprosarium (87%) [15] and Aboriginal and Torres Strait Islander communities in Australia [16–18].

The Pacific Region is particularly affected by scabies, and consequently related morbidity is high. For example, in a school in Timor Leste, an overall prevalence of 22% was detected, with 45% in 20–24 year-olds [19]. A census including six island communities in Fiji evidenced a prevalence of 36% in the general population, and 56% in 5–9 year-olds [20].

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12.2 Morbidity and Characteristics of Scabies in Resource-Poor Communities

While the diagnostic features are similar (Figs. 12.1 and 12.2), morbidity and clinical features in resource-poor communities are considerably different from those in high-income settings, leading to high prevalences and severe morbidity (Box 12.1) [3, 6, 21–23]. As a consequence of persisting high preponderance, intense itching and pain leading to sleep disturbances, and secondary bacterial infection causing impetigo, abscess formation, and lymphadenopathy is common [3, 12–14]. Usually, all age groups are affected, but children are among the most afflicted with a severe morbidity burden (Fig. 12.3) [9, 22, 24–26]. Group A streptococcal pyoderma may cause post-streptococcal glomerulonephritis and acute rheumatic fever [6, 27–29]; these latter aspects will be dealt with specifically in Chap. 13.

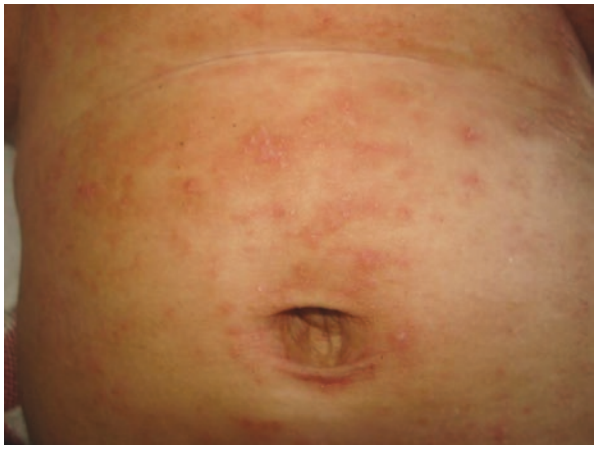

Fig. 12.1 Papules on the abdomen of a scabies patient

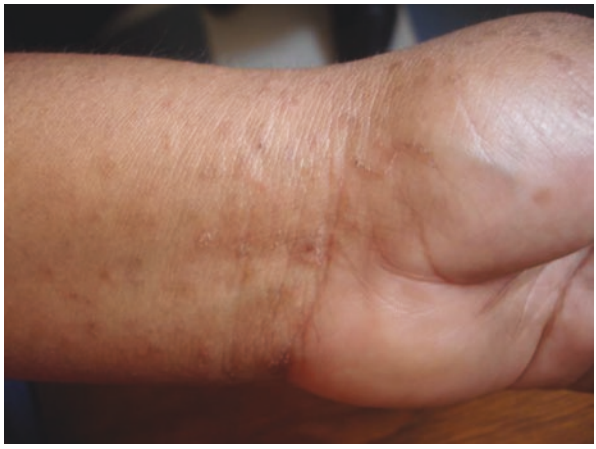

Fig. 12.2 Papules and evident diagnostic burrows on the wrist of a patient with scabies

Box 12.1 Typical Features of Scabies in Resource-Poor Communities

Poverty
Crowding, precarious living and hygiene conditions
Deficient health care system
Delayed diagnosis, limited treatment options, no community control measures
↓
High prevalence
Long-term and persistent infestations
Children most heavily affected
Bacterial superinfection
↓
Severe itching
High rates of skin infections, impetigo, pyoderma, abscesses
Lymphadenopathy (mostly inguinal)
Sleep disturbances (mostly due to itching and pain)
Quality of life negatively affected
Social stigmatization
Other morbidities and sequels (Acute Rheumatic Fever, Post-Streptococcal Glomerulonephritis)

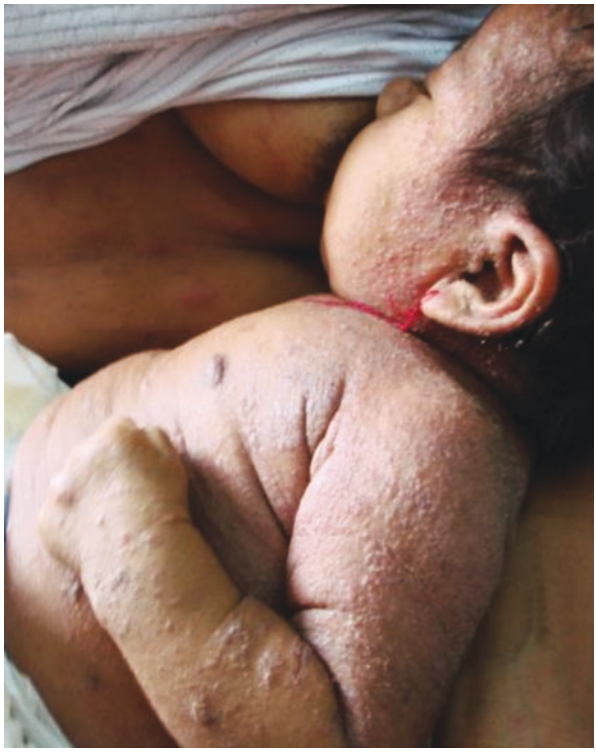

Fig. 12.3 Child with severe infestation (crusted scabies) after chronic use of topical steroids

One of the major problems in poor settings is the aggravation of scabies with the use of immunosuppressive drugs, such as high potency topical steroids either combined with antibiotics and antimycotics, or as a single treatment, as they are commonly sold as over-the counter treatments [11]. It is not infrequent that patients request recommendations to pharmacists, other patients, or general practitioners with low experience in the diagnosis of skin diseases, who erroneously recommend such treatments, which consequently cause a quick first relief of symptoms. However, as the underlying cause is not solved, secondary effects become evident after chronic use, like hirsutism, striae, skin atrophy, telangiectasia, and Cushing syndrome, or in severe cases crusted scabies, a severe infestation with thousands of scabies mites [30].

In endemic communities, there is often reluctance of treatment of the families and contact persons of an index case. Family members may have asymptomatic scabies or are still in the incubation period, which can cause undetected but considerable dissemination of the disease to other family members. This is particularly important when children are under the care of grandparents or other family members such as elder siblings. In addition, common co-morbidities in these settings, such as diabetes, malnutrition or other immunosuppressive health conditions may influence the clinical lesions and symptoms.

12.3 Itching and Secondary Bacterial Infections

In the context of scabies, the itching is an allergic immune response to mite products, and occurs in a majority of the affected individuals [1, 2, 27, 31]. Intense itching and scratching result in skin damage and facilitate secondary bacterial infection, and subsequently impetigo and pyoderma [3, 22, 28, 32, 33]. In fact, bacterial skin infection is very common in communities with endemic scabies, especially in resource-limited settings in the Pacific Region and Australian Aboriginal communities [26, 34–36]. In East Timor, impetigo in students with scabies was observed in 21.5%, as compared to 6.4% in those without scabies [19]. In Fiji, impetigo was observed in 23.4% of the general population, with a 2.6-fold risk in those with a diagnosis of scabies; 36% of impetigo cases were attributed to scabies in these highly affected communities [20]. Lymphadenopathy is also correlated to secondarily-infected scabies lesions [8, 22], and high proportions occur in affected populations [1, 27].

12.3.1 Sleep Disturbances and Socio-Emotional Aspects

Severe itching has been reported to induce sleep disturbances in scabies-affected individuals. Two thirds to three quarters of scabies patients in resource-poor communities in Nigeria and Brazil have reported sleep disturbances due to scabies [1, 37]. Socio-emotional aspects of play a significant role for affected people's quality of life. In an urban slum in Brazil, about 80% of scabies-infested individuals stated

that their quality of life was affected by scabies [38]. Shame, impact on leisure activities and perceived stigmatization were also very common.

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13 Morbidity of Scabies in Resource-Limited Countries: Rheumatic Heart Disease (RHD) and Post-Streptococcal Glomerulonephritis (APSGN)

Anita Smith, Anna Schauer, Jonathan R. Carapetis, Wendy Hoy, James McCarthy, and Asha C. Bowen

13.1 Introduction

13.1.1 Introduction: The Links Between Scabies and Group A Streptococcus (GAS)

Scabies is one of the world's most prevalent diseases with approximately 147 million cases (global point prevalence) and an estimated annual incidence of 455 million cases [1]. Prevalence has been reported to be highest in hot and humid climates,

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such as Island communities in the Pacific region, central America and Indigenous communities of Northern Australia [2]. Scabies is one of the most significant neglected tropical diseases and accounts for an estimated 3.8 million disability-adjusted life years [1].

Sarcoptes scabiei var. *hominis* is an ectoparasite causing scabies infection which manifests as severe pruritus, skin lesions and further complications due to the secondary bacterial infection with *Streptococcus pyogenes* (also known as Group A Streptococcus) and *Staphylococcus aureus*. The clinical features of scabies are severe pruritus and the presence of multiple erythematous papules, often with excoriations. Classically involved sites include the wrists, fingers, feet, elbows, knees, buttocks, male genitalia and axillae. It is also possible to view burrows, particularly in web spaces.

Scabies transmission occurs via skin-to-skin contact between humans. There is no non-human reservoir for scabies infection [2], and in the absence of a human host, the scabies mite does not survive beyond 2 days [3]. Scabies transmission is most common in settings where people live together in close proximity [4] and have reduced access to hand and washing facilities for clothing.

These environmental and socioeconomic conditions are similar to those where acute rheumatic fever (ARF) and subsequent rheumatic heart disease (RHD) are also prevalent. In a cross-sectional study prospectively assessing skin infections in 158 children admitted to regional hospitals in Australia [5], the prevalence of scabies and impetigo were respectively 8.2% and 49.4%. ARF, severe soft tissue and skeletal infections and acute post-streptococcal glomerulonephritis (APSGN) accounted for 24.1% of total hospital admissions during this period. Furthermore, a diagnosis of scabies in hospital has been found to be associated with a subsequent ARF diagnosis [6].

Given the association of scabies with GAS secondary infection, and the causal role GAS plays in the pathogenesis of rheumatic fever, it has been hypothesised that scabies facilitates the introduction of GAS skin infection and is a link in the pathway towards ARF.

13.1.2 Secondary Infection of Scabies Lesions

Secondary infection with the bacterial pathogens *S. pyogenes* and *S. aureus* is a well-recognised complication of scabies infection. The nomenclature for secondarily infected scabies includes a variety of terms such as pyoderma, impetigo, skin sores, school sores and impetiginised scabies – which are all used interchangeably below depending on the source dataset. In tropical environments, there is a strong association between impetigo and scabies infection [7]. Scabies and secondary bacterial infection may be considered largely interdependent. The pruritus associated with scabies is caused by a hypersensitivity reaction to constituents in the faecal material, eggs and saliva of the scabies mite. Scratching breaks down the epidermis with further excoriations enabling access of pathogenic bacteria resulting in

secondary infection [8–12]. Pyoderma is a common complication of scabies, especially in patients with numerous scabietic lesions [11]. Secondary bacterial infections may also result in abscess formation, cellulitis, joint and bone infections and sepsis. Skin infections may also lead to acute rheumatic fever [13] and post-streptococcal glomerulonephritis [14].

Rates of scabies and impetigo in Oceania are among the highest in the world [15, 16]. Whilst the reported prevalence of impetigo ranges from 0.2% to 90%, the highest median prevalence has been reported in Oceania (40.2%, IQR 17.2%–48.1%) [15]. Similarly, for scabies, the highest median prevalence was again reported in Oceania with a median prevalence of 16.0% (IQR 4.9%–25.0%) [15]. In contrast, the median prevalence for scabies in Africa was 2.0% (IQR 0.7%–7.0%) and in Asia the scabies median prevalence was 3.4% (IQR 0.9%–11.9%). It was also noted that there appeared to be a close correlation between the prevalence of scabies and pyoderma ($p = 0.01$) [15].

In a systematic review conducted by Romani et al. [16], 26 studies recorded impetigo prevalence. Across these studies, impetigo prevalence was noted to be high specifically in the Solomon Islands (43%) [17] and in Northern Australian Indigenous Communities (49%) [18]. It was noted that scabies and impetigo both had a higher prevalence in children compared to adults [16]. In an Australian study by Carapetis et al. [18] the prevalence of impetigo in children aged less than 16 years was 69%. Similarly, in other countries such as Vanuatu (16%), Fiji (36%) and the Solomon Islands (52%) a higher prevalence of impetigo was also noted in children [7, 17, 19]. Overall, Romani et al. [16] concluded that across studies, the prevalence of impetigo did not strongly correlate with the prevalence of scabies; however, this relationship was not formally assessed. This was surprising to the authors, and potentially due to the underdiagnosis of scabies or overestimation of impetigo, with further research recommended using consistent methodology across populations to accurately assess this correlation [16].

In Indigenous children in the Northern Territory of Australia, GAS impetigo is very common. In Indigenous children, the prevalence of impetigo and scabies co-infection (data from a Northern Territory Randomised Controlled Trial investigating impetigo treatment in remote communities) reported the prevalence of clinically diagnosed scabies in children randomised for treatment of impetigo to be 16.5% [20]. The use of cotrimoxazole in the treatment of impetigo [21] may have positively impacted the resolution of scabies, and further work is needed to elucidate this [20].

In Fiji, a study of prevalence showed a strong association between scabies and impetigo, with an estimated population attributable risk of 93% [22]. Data from the SHIFT trial, a mass drug administration trial of ivermectin compared to permethrin or standard care for scabies, found the scabies prevalence at baseline was 32.1%, 41.7% and 36.6% at baseline across each of the three groups respectively [23]. Impetigo prevalence was between 21.4% and 24.6% (Table 13.1) prior to treatment. One year post treatment, the prevalence of impetigo decreased across all treatment groups with a relative reduction in the prevalence of impetigo increasing from 32%

Table 13.1 Prevalence of scabies and impetigo at baseline and 12 months post-treatment[a]

	Prevalence at baseline		Prevalence at 12 months		Absolute reduction in prevalence	Relative reduction in prevalence
Study group	No./total no.	% (95% CI)	No./total no.	% (95% CI)	Percentage points (95% CI)	% (95% CI)
Ivermectin						
Scabies	230/716	32.1 (28.8–35.6)	11/587	1.9 (0.9–3.3)	30.2 (26.6–33.9)	94 (83–100)
Impetigo	176/716	24.6 (21.6–27.9)	47/587	8.0 (6.1–10.5)	16.6 (12.7–20.4)	67 (52–83)
Permethrin						
Scabies	222/532	41.7 (37.6–46.0)	71/449	15.8 (12.6–19.5)	25.9 (20.4–31.2)	62 (49–75)
Impetigo	131/532	24.6 (21.2–28.5)	51/449	11.4 (8.8–14.6)	13.3 (8.5–17.9)	54 (35–73)
Standard care						
Scabies	294/803	36.6 (33.4–40.0)	140/746	18.8 (16.0–21.8)	17.8 (13.4–21.5)	49 (37–60)
Impetigo	172/803	21.4 (18.7–24.4)	109/746	14.6 (12.3–17.3)	6.8 (3.0–10.6)	32 (14–50)

.

Reproduced with permission from SHIFT trial [23]

[a]The absolute reduction is the difference between the prevalence at 12 months and the prevalence at baseline, and the relative reduction is the ratio of the prevalence at 12 months to the prevalence at baseline. CI denotes confidence interval

(95% CI 14–50) with standard care to 54% (95% CI 35–73) with permethrin and 67% (95% CI 52–83) with ivermectin treatment. The correlation between scabies and impetigo in terms of prevalence at baseline, as well as the parallel decline in prevalence of both in response to treatment of scabies implies a strong association between scabies and impetigo.

Treating scabies at a community level in endemic settings has been demonstrated to reduce the prevalence and severity of skin sores. Single-arm trials of mass drug administration of either ivermectin or permethrin [24–27] have shown the effectiveness of mass drug administration in controlling scabies. Additionally, the SHIFT trial [23], further supported mass drug administration, demonstrating that ivermectin was more effective than permethrin [23] in controlling both scabies and impetigo. In addition, these mass drug administration trials also showed significant reductions in the prevalence of impetigo after treatment of scabies at a community level [28].

13.1.3 Group A Streptococcal Pharyngitis Precedes Acute Rheumatic Fever: *An Overview*

GAS infections have long been implicated in the development of Acute Rheumatic Fever (ARF) (Fig. 13.1). Epidemiological and laboratory evidence collected over more than 60 years supports the role of GAS throat infection preceding ARF, although data are mostly from settings where GAS skin infections are not common [30]. Indirect associations between high prevalence of GAS skin sores and ARF in regions with low incidence of pharyngitis suggested that skin sores also contribute to the onset of ARF [30]. The Rheumatic Heart Disease Australia Guidelines (3rd Edition) were recently updated, and for the first time include treatment of pharyngitis and skin sores for primary prevention of ARF [31].

Until recently, GAS pharyngitis was considered to be the only antecedent cause of ARF. For nearly a century, the link between pharyngitis and ARF has been recognised. This was based on observations from outbreaks of ARF which closely followed epidemics of GAS pharyngitis, or pharyngitis in association with scarlet fever. Reports dating back to the early 1900s demonstrated that throat infections with GAS such as tonsillitis in sub-clinical or clinical forms predate and are associated with ARF. Further, a 70% reduction in the incidence of ARF with appropriate treatment of GAS pharyngitis has been demonstrated. In 1954, Catanzaro et al. showed that early treatment of streptococcal A sore throats (within 9 days of symptom onset) prevents ARF [32]. Management of GAS throat infections has been well documented, with particular emphasis on primary prevention of ARF [31–34].

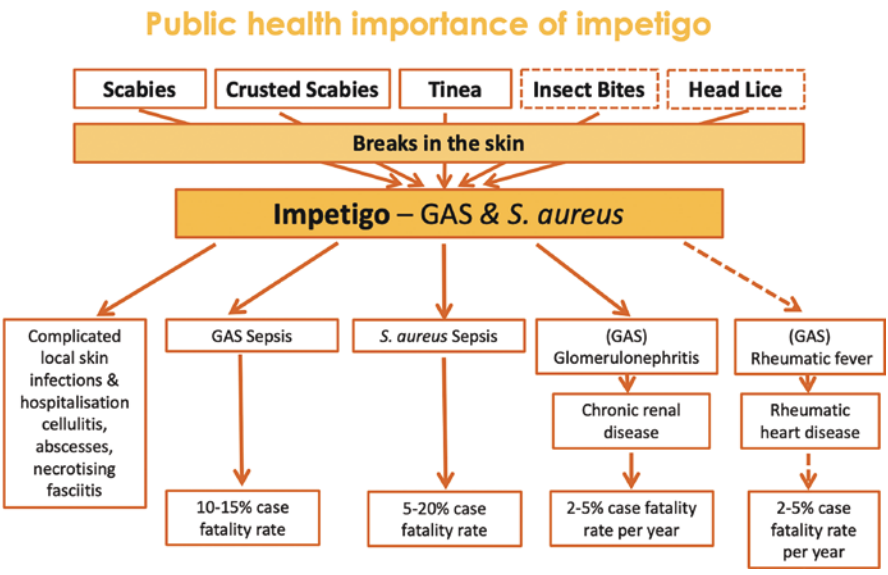

Fig. 13.1 Complications of scabies infection. (Reproduced with permission from National Healthy Skin Guidelines, The Australian Healthy Skin Consortium, 2018) [29]

Whilst GAS pharyngitis as an antecedent cause of ARF is proven, and is likely to be responsible for all, or the vast majority, of ARF cases in certain geographic regions, the link in other high disease-burdened areas is not as straightforward. Up to 20% of school-age children may be colonised with GAS in the oropharynx in temperate climates [35]. In tropical climates, however, less than 5% carry GAS in the oropharynx, with groups C and G streptococci being more common. The rate of throat colonisation of GAS in remote Northern Territory communities has been reported as <5% [30], whilst in urban areas this has been reported as being three times higher at 15% [36]. In a recent meta-analysis, GAS pharyngeal carriage rates of 10.5% (95% CI 8.4–12.9) in high-income countries and 5.9% (95% CI 4.3–8.1) in low-middle income countries have been found [37]. Yet, there are a exceptions: a recent cross-sectional study by DeWyer et al. [38], investigating GAS pharyngeal carriage in children aged 5–16 years in Uganda showed that the rates were higher (15.9%) compared to pooled global rates (12%). In addition, this study also showed higher rates (41.8%) of GAS positive sore throat [38].

13.1.4 Does GAS Skin Infection Result in ARF?

GAS is commonly cultured from impetigo and secondarily infected scabies lesions. The observation of low rates of pharyngitis and high rates of scabies and impetigo in regions with the highest reported burden of ARF, has led to the hypothesis that skin infection may contribute to the development of ARF [30]. This has been further substantiated through data from Oceania where there is a strong epidemiological association between skin infections and rheumatic fever [21, 22, 39, 40].

Specific characteristics of *S. pyogenes* have been shown to be influential in the host-bacteria interactions resulting in autoimmunity and ARF development. The M protein gene (*emm*) encodes the cell surface M virulence protein. As there are at least 100 *S. pyogenes* M serotypes and *emm alleles,* typing is used to differentiate these different M serotypes. The underlying basis of this dates back to ARF epidemics in soldier recruits in World War II, where certain GAS strains were found to have abundant M protein and were encapsulated by hyaluronic acid [41]. This led to the concept of rheumatogenic M serotypes such as 3, 5, 6, 18, 19 and 24 [41].

More recently, the proposal that a minority of GAS *emm* types are more "rheumatogenic" than others has been called into question [42, 43]. In particular, the GAS strains isolated in tropical climates where ARF is endemic have been found to be highly divergent. These GAS strains are more diverse and are dominated by skin-associated strains, further adding weight to the possibility that skin-associated GAS strains are linked to ARF [44]. These skin-associated strains have been characterised via refined typing methodology. *Emm pattern-typing* distinguishes distinct chromosomal architectures for GAS. Emm pattern A–C strains have been classified as throat specific, whereas emm pattern D strains display skin tropism and emm pattern E strains may be found at both sites [45]. Williamson et al. (2016) characterised the GAS strains from pharyngitis and skin infections in New Zealand among

children at high risk of ARF and reported that the large proportion of *emm* were pattern D strains in skin and pharyngeal isolates, supporting the proposed role of skin infections in ARF pathogenesis [46].

The link between GAS infections and ARF may be illuminated by looking at epidemiological data from Indigenous communities of Northern Australia. In the Northern Territory of Australia, in Indigenous people, rates of ARF (354 per 100,000 people in 2017) and RHD (2436 per 100,000 people) are among the highest in the world [47]. GAS pharyngitis, however, is uncommonly reported and often there is no history of an antecedent sore throat. In a prospective surveillance study by McDonald et al. [48] in three remote Indigenous communities, there was a very low incidence of sore throat (8 cases per 100 person-years (95% CI, 4–15 cases) and no symptomatic GAS pharyngitis cases, despite a particularly high incidence of ARF. Further studies to explore this hypothesis in are currently underway among Indigenous Australian children in the Kimberley, WA. In a recent publication using molecular point-of-care detection of GAS more GAS than expected from previous studies was isolated in the throats; this needs to be validated in a larger sample size [49]. Similarly, in Pacific Island populations, ARF and scabies rates are high [16].

The link between skin infection and ARF has been considered by Australasian researchers to involve scabies infection as an antecedent to ARF [6, 29]. There is a high prevalence of skin infection, scabies and rheumatic fever which coexist in many Pacific Island nations and Australian Indigenous populations. Scabies infection may lead to streptococcal cellulitis, and rheumatic fever is caused by GAS. A data linkage study in New Zealand reported that there was a strong epidemiological association between ARF and scabies infection [6].

The identification of scabies in populations at high risk of ARF is important. Early recognition and treatment of scabies may reduce the risk of ARF developing. Whilst often underappreciated as being benign skin problems, scabies and GAS impetigo have a trajectory to chronic illness and premature demise through the association with ARF and subsequent RHD. In 2013, the WHO identified scabies as a neglected tropical disease [50]. Ongoing efforts in individual treatment and public health control through mass drug administration may have an impact on RHD control globally.

Molecular mechanisms that may allow scabies infections to promote GAS infection in skin lesions have been described by Fischer et al. [51]. These include novel and unexpected proteins that appear important to mite survival and evasion of the host defence. Further studies are required to determine the causal link between GAS impetigo and ARF/RHD.

13.1.5 Conclusions

Scabies represents one of the world's most significant neglected tropical diseases with substantial morbidity and long-term sequelae. Secondary infection, as identified its many forms – pyoderma, impetigo, skin sores and school sores – is a

common, expected and under-recognised complication. The significance of this infection has only recently been realised. Whilst the traditional dogma is that streptococcal pharyngitis precedes ARF, there is increasing credence to GAS skin infection as a precipitant to ARF. This is supported by epidemiological data and GAS molecular typing studies, with high rates of impetiginised scabies in ARF endemic regions throughout the world.

13.2 ARF & RHD

13.2.1 What Is ARF? Natural History, Diagnosis and Treatment

Acute rheumatic fever (ARF) may present in various ways within weeks of a GAS infection, either pharyngitis or possibly following impetigo and scabies.

The hallmark features of ARF include fever, arthritis, carditis, chorea, erythema marginatum and subcutaneous nodules. The different manifestations are classified as either major or minor criteria as per the revised Jones criteria [52].

The Jones criteria including clinical and laboratory criteria is used to confirm a primary episode of ARF (Table 13.2) [53]. The criteria originally developed in 1944 have been regularly revised to ensure that in situations where the incidence is reducing, the positive predictive value is preserved [53]. However, in scenarios where

Table 13.2 Updated Australian guidelines for ARF diagnosis (used with permission of the copyright owner (the original publisher)

	High-risk groups[a]	Low-risk groups
Definite initial episode of ARF	2 major manifestations + evidence of preceding Strep A infection *or*	
	1 major + 2 minor manifestations + evidence of preceding Strep A infection[b]	
Definite recurrent[c] episode of ARF in a patient with a documented history of ARF or RHD	2 major manifestations + evidence of preceding Strep A infection, *or*	
	1 major + 2 minor manifestations + evidence of preceding Strep A infection[b], *or*	
	3 minor manifestations + evidence of a preceding Strep A infection[b]	
Probable or possible ARF (first episode or recurrence[c])	A clinical presentation in which ARF is considered a likely diagnosis but falls short in meeting the criteria by either:	
	• One major or one minor manifestation, *or*	
	• No evidence of preceding Strep A infection (streptococcal titres within normal limits or titres not measured)	
	Such cases should be further categorised according to the level of confidence with which the diagnosis is made:	
	• Probable ARF (previously termed 'probable: highly suspected')	
	• Possible ARF (previously termed 'probable: uncertain')	

Table 13.2 (continued)

	High-risk groups[a]	Low-risk groups
Major manifestations	Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram)	Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram)
	Polyarthritis[d] or aseptic monoarthritis or polyarthralgia	Polyarthritis[d]
	Sydenham chorea[e]	Sydenham chorea[e]
	Erythema marginatum[f]	Erythema marginatum[f]
	Subcutaneous nodules	Subcutaneous nodules
Minor Manifestations	Fever[g] ≥38 °C	Fever ≥ 38.5 °C
	Monoarthralgia[h]	Polyarthralgia or aseptic monoarthritis[h]
	ESR ≥30 mm/h or CRP ≥ 30 mg/L	ESR ≥ 60 mm/h or CRP ≥ 30 mg/L
	Prolonged P-R interval on ECG[i]	Prolonged P-R interval on ECG[i]

CRP C-reactive protein, *ECG* electrocardiogram, *ESR* erythrocyte sedimentation rate

[a]High-risk groups are those living in communities with high rates of ARF (incidence >30/100,000 per year in 5–14-year-olds) or RHD (all-age prevalence >2/1000). Aboriginal and Torres Strait Islander peoples living in rural or remote settings are known to be at high risk. Data are not available for other populations but Aboriginal and Torres Strait Islander peoples living in urban settings, Mäori and Pacific Islanders, and potentially immigrants from developing countries, may also be at high risk

[b]Elevated or rising antistreptolysin O or other streptococcal antibody, or a positive throat culture or rapid antigen or nucleic acid test for Strep A infection

[c]Recurrent definite, probable or possible ARF requires a time period of more than 90 days after the onset of symptoms from the previous episode of definite, probable or possible ARF

[d]A definite history of arthritis is sufficient to satisfy this manifestation. Note that if polyarthritis is present as a major manifestation, polyarthralgia or aseptic monoarthritis cannot be considered an additional minor manifestation in the same person

[e]It Chorea does not require other manifestations or evidence of preceding Strep A infection, provided other causes of chorea are excluded.\

[f]Care should be taken not to label other rashes, particularly non-specific viral exanthems, as erythema marginatum

[g]In high-risk groups, fever can be considered a minor manifestation based on a reliable history (in the absence of documented temperature) if anti-inflammatory medication has already been administered

[h]If polyarthritis is present as a major criterion, monoarthritis or arthralgia cannot be considers an additional minor manifestation

[i]If carditis is present as a major manifestation, a prolonged P-R interval cannot be considered an additional minor manifestation

there is a high burden of disease, some have opted to modify the revised criteria to maintain the negative predictive value and sensitivity [54].

The most common presentation of ARF involves an acute febrile illness with arthritis and often carditis. Less common presentations include chorea and insidious carditis as manifestations of ARF in the absence of other features.

13.2.2 RHD and Long-Term Consequences

Secondary prophylaxis to prevent recurrent GAS infections, and rheumatic fever, is aimed to reduce the progression to RHD. Whilst RHD may still progress with secondary prophylaxis, it is more likely to progress without. Severe or recurrent episodes of ARF lead to progressive damage of the heart valves, particularly the mitral valve (and occasionally the aortic valve) resulting in valvular dysfunction and progressive heart failure. Surgical intervention to repair or replace affected valves, as well as medical management of heart failure, is often required. In the absence of effective medical and surgical management, premature demise is likely. Indigenous Australians with RHD who passed away during 2014–2018 had a median survival from diagnosis of 11 years, and one-third were aged between 15 and 44 years [55].

In low- and middle-income countries, the first diagnosis of ARF may in fact be RHD with severe cardiac failure secondary to mitral valve damage. In such settings without access to surgical management, death may be rapid [56].

13.2.3 Morbidity and Mortality of Rheumatic Heart Disease (RHD)

RHD remains an important preventable cause of cardiovascular death and disability. RHD is the leading cause of heart disease in children in developing countries and is a major cause of disease in adults as well. It contributes to a significant proportion of GAS related morbidity and mortality. RHD and its complications are thought to represent two thirds of GAS-related deaths each year [57].

The global prevalence of RHD is not well defined. It is estimated that 39.3 million people worldwide are affected by RHD, with approximately 285,517 deaths occurring each year [58]. In developed regions, as living standards have improved, the incidence of RHD has greatly diminished. The notable exception to this being that is remains exceedingly high among Indigenous populations of Australia and New Zealand [59–61].

RHD affects young people, leading to premature morbidity and mortality. Estimates based on cardiac auscultation suggest that at least 1.3 per 1000 school-aged children in developing countries are affected. The use of echocardiography, however, indicates that the prevalence of RHD is at least ten times higher by detecting latent cases of RHD not evident by standard auscultation [62]. Clearly, given the excessive burden of disease and significant complications, there warrants an urgent need for effective detection, control and prevention of ARF and RHD.

13.2.4 Link Back to Scabies

In a study of patients in Trinidad Potter et al. [63] investigated ARF or APSGN during an outbreak of scabies and secondary impetigo, reporting that streptococcal strains colonising the skin of patients with impetigo were different to those

associated with ARF, and were not the strains found in the pharynx. As described above, this is a similar observation to that seen in Australian Indigenous populations [48] and Pacific Islands [7]. A study of over 200,000 children (aged 3–12 years) followed over a mean time of 5.1 years found that children diagnosed with scabies were 23 times more likely to develop ARF or chronic RHD compared to children who were not diagnosed with scabies [6].

Some have speculated that Groups C and G streptococcus may also contribute to ARF in these populations. This is because although Groups G and C streptococci have been commonly identified in the throat of Indigenous people, and they have less commonly been identified in pyoderma lesions [64]. Further research is required to investigate the potential association between non-GAS strains and rheumatic fever, as they may have common antigens with GAS that are important in initiating ARF.

13.3 Acute Articular Rheumatism

13.3.1 History and Examination

Joint symptoms (arthritis) are often the presenting feature of ARF. Arthritis usually manifests within 21 days of a GAS infection. However, in some cases, cardiac symptoms (carditis) may present first. Arthritis may be more intense in adolescents and young adults compared to children [65].

Typically, each joint is inflamed for a period of 1 day to a week with numerous joints involved in swift succession. Joints in the legs are generally the first affected. Elbows, wrists, knees and ankles are commonly affected [66]. The migratory nature of the arthritis is typical, hence the description of ‘migratory polyarthritis’. Arthritis may limit movement in some severe cases. Generally, joint pain outweighs any objective signs of inflammation and is transient.

13.3.2 Pathogenesis

Activation of the innate immune system by a GAS pharyngeal infection, results in GAS antigen processing and presentation to T and B cells (Fig. 13.2) [44]. The T- and B-cell response includes $CD4^+$ T-cell activation and immunoglobulin production.

Joint tissue is believed to be involved through molecular mimicry between the GAS group A carbohydrate or the M protein (serotype-specific). This cross-reactive immune response can result in the formation of immune complexes leading to transient arthritis.

13.3.3 Investigations

Imaging via X-ray is not commonly performed as is generally unremarkable, although may reveal a slight effusion of an affected joint. In the case of a significant effusion, aspiration of synovial fluid for analysis and culture is recommended to

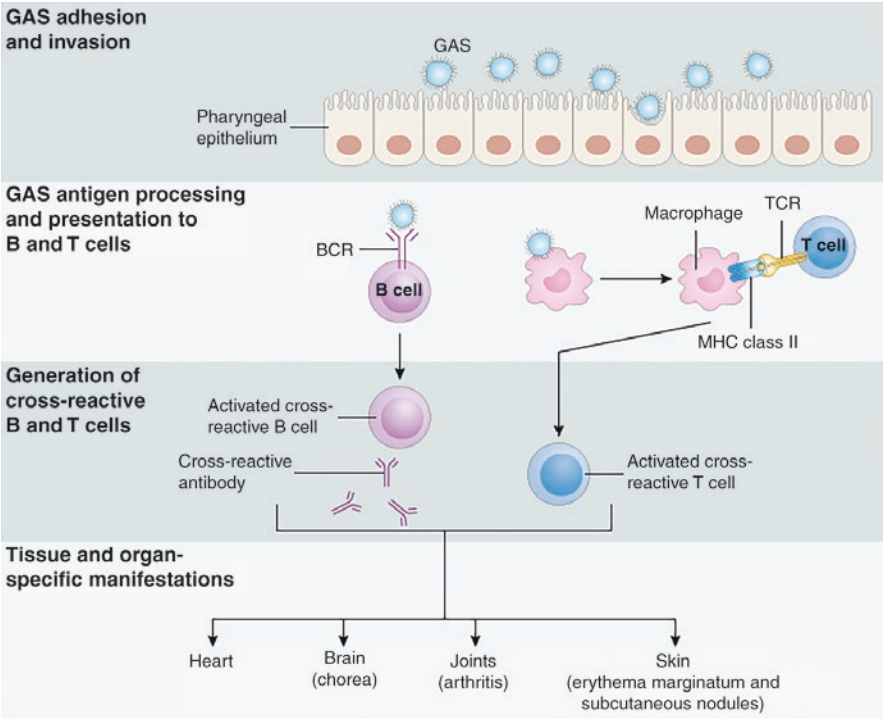

Fig. 13.2 Immune response in acute rheumatic fever. Joint tissue can be involved through molecular mimicry between the GAS group A carbohydrate or the M protein (serotype-specific). *GAS* group A streptococcus, *BCR* B-cell receptor, *TCR* T-cell receptor, *MHC* major histocompatibility complex. (Reproduced from Carapetis et al. [44] with permission of the copyright owner (the original publisher))

differentiate it from septic arthritis, or where there is a significant effusion affecting only one joint. Results of synovial fluid analysis in ARF typically show a sterile inflammatory pattern. This is an important consideration in the possible association between scabies and ARF. Differentiating septic arthritis from ARF is of paramount importance as management is different.

13.3.4 Management

In ARF, the natural history can be modified by steroids and anti-inflammatory drugs which typically results in remission of arthritis in the affected joints and termination of the migration of arthritis to other joints. As such, patients treated with non-steroidal anti-inflammatory drugs early in the illness may have monoarthritis and never progress to polyarthritis. For example, in a study of 555 Indigenous patients, 17% of cases had monoarticular arthritis (aseptic) [67]. This can however cloud the picture, making it challenging to accurately diagnose ARF which may mean

children in need of secondary prophylaxis are not identified. If within 2 days there is no response to non-steroidal anti-inflammatory drugs, alternative diagnoses should be considered.

Alternative therapies such as symptomatic analgesia with paracetamol can be indicated in cases of monoarthritis where ARF is suspected. Once a second joint is involved, and the diagnosis is more convincing, non-steroidal anti-inflammatories can be started. Without treatment, arthritis resolves in approximately 4 weeks with no long-term joint deformity.

13.4 Acute Post-Streptococcal Glomerulonephritis (APSGN)

13.4.1 Introduction

Acute post-streptococcal glomerulonephritis (APSGN) is characterised by haematuria, albuminuria and oedema; often complicated by hypertension and acute renal failure [68]. The long-term outcomes of APSGN are variable, ranging from no sequelae through to chronic kidney disease, with associated hypertension. A review of 229 children following APSGN from three case series revealed that between 5 and 18 years after presentation, >92% of children had moderately reduced or normal renal function [69].

Evidence supporting the evolution to chronic kidney disease as a consequence of APSGN without essential hypertension or diabetes comes from an Australian study of 200 Indigenous children. Each had at least one episode of APSGN associated with GAS skin infection (often scabies related); these children were 3–4 times more likely compared to children without history of APSGN to have significant albuminuria 5 years (or more) later [70]. Additional studies have confirmed that in follow-up of APSGN patients 10–40 years after the acute episode, many suffer from renal impairment, hypertension and recurrent proteinuria [71–74].

13.4.2 Epidemiology: APSGN Link to Scabies Globally

The association of skin infections, in particular scabies, and APSGN has been recognised for several decades, spanning several continents. One of the earliest reports came from an outbreak of APSGN in Red Lake Minnesota, North America in 1964 where "over half of the children were suspected of having scabies with secondary infection." Additionally, in children with throat and skin infections, sporadic cases of APSGN were also reported [75].

Since the 1970s, scabies epidemics with ensuing cases of APSGN have been described. In Trinidad, in a study undertaken by Svartman et al. [76], β-haemolytic streptococci were isolated from skin lesions characteristic of scabies during a large epidemic of APSGN. Of 139 patients with APSGN, 51% had scabies. Of the 71 patients with nephritis and scabies, 63% had GAS cultured from their skin lesions, whilst 59% of the 34 patients without scabietic lesions skin cultures were also

positive. The frequency of GAS in throat cultures was significantly lower than in skin lesions in all study groups. It was observed that the scabies mite represented an attractive site for streptococcal infection, as indicated by the high percentage of infected lesions, and that scabietic lesions probably represented a greater risk factor for developing APSGN than other forms of skin infections. The multiple persisting scabietic lesions provided more opportunity for GAS infection. In six family members with scabietic lesions, all were found to have laboratory signs of sub-clinical APSGN (including decreased serum beta 1C), indicating that these lesions provided a suitable environment for inciting nephritogenic factors [76].

The association between scabies and APSGN has also been reported in Africa. In Livingston Hospital (South Africa), of 75 consecutive cases with APSGN admitted to hospital over a 2-year period between 1962 and 1964, 44 (60%) had scabies; 12 (16%) had other skin infections (26 impetigo and 5 septic ulcers) and 19 (4%) had no skin disease. Other findings including cardiac decompensation were more common in the scabies group. Renal impairment was less common in the scabies group and hypoalbuminaemia persisted for longer in children with other skin infections [77]. Turnbull et al. [78] reported data from 4695 admissions to a mission hospital in Southern Africa between June 1971 and May 1972. They identified 22 patients with APSGN, 14 (43%) suffering from infected scabies, 9 (27%) with a history of recent URTI and 2 (6%) with impetigo. The remaining eight (24%) gave no history of recent infection, although some of them had uncomplicated scabies. The authors concluded that "acute glomerulonephritis secondary to a pyoderma and especially septic scabies, may in some areas be very common" [78] (Table 13.3).

Tasic et al. [79] reported that family contacts of index cases have higher rates of sub-clinical nephritis. In this study, 75 families with index cases of APSGN were screened for the presence of sub-clinical disease. In 170 siblings, 9.4% had nephritis and 22.3% had an abnormal urinalysis, whilst no features of APSGN detected among the 147 parents screened (Table 13.4).

Table 13.3 Frequency of Group A BHS in throat and skin lesions among Trinidad study groups related to the presence of scabies [76]

Study group	% with group-A B.H.S. in skin lesion				% with group-A B.H.S. in throat			
	Of subjects with lesions			Of all subjects (both with and without lesions)	Of subjects with lesions			Of all subjects (both with and without skin lesions)
	Scabies	Other	Either		Scabies	Other	None	
Nephritis patients	63	59	62	*47*	27	18	18	*23*
Family members	69	70	70	*39*	25	30	14	*21*
School-children Villagers	50	72	66	*28*	7	11	14	*12*
	93	84	89	*31*	28	36	13	*20*

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Numbers of subjects shown in italic type

Table 13.4 Features of index cases of acute post-streptococcal glomerulonephritis [80]

	n	%
Presenting symptoms		
Puffy face	7	64
Skin sores	3	17
Dark urine	2	18
Initial examination findings		
Infected scabies	7	64
Facial oedema	8	73
Hypertension	11	100
Haematuria	11	100
Proteinuria	11	100
Recent treatment with intramuscular penicillin	3	27
Initially diagnosed with 'food allergy'	2	18
Household contact	1	9
Evacuated due to complications	11	100

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Outbreaks of APSGN occur sporadically in remote Indigenous communities in Australia [80]. In a study of a remote Indigenous community in Far North Queensland (Australia) where 87 children were screened during 2006, 46% had infected scabies, and 11 cases of APSGN were detected over 4 months. Infected scabies was the main preceding finding in these children [80]. APSGN outbreaks were reported to have a 5–7-year cycle in the Northern Territory [14]. Whether this is linked to patterns of scabies infections or to the introduction of new GAS strains causing impetigo is unknown. A similar pattern has not been seen in the Kimberley, WA, where APSGN outbreaks have been infrequent.

Impetigo among Indigenous children in remote Australia has been reported to have the highest prevalence in the world. Studies spanning four decades consistently report prevalence above 40% [15, 81]. Impetigo is predominantly caused by GAS [40, 82] and associated with scabies [20]. Elevated background streptococcal titres in the serum consistent with this have been reported [82, 83].

13.4.3 Pathogenesis of APSGN and Contribution of Scabies

The association of skin infections with acute glomerulonephritis has been recognised for several decades. Proposed mechanisms for the pathogenic link between scabies and APSGN include streptococcal superinfection of skin lesions vs. involvement of a scabies mite mediated immunocomplex. Both may be required.

13.4.3.1 Acute GN Caused by Secondary Bacterial Infection

A delay in treatment of scabies may lead to an increased risk of secondary bacterial infections and/or septicaemia followed by PSGN. Scabies and bacterial infection may be largely interdependent. Pruritus is caused by a hypersensitivity reaction to constituents in the faecal material, eggs and saliva of the scabies mite. Scratching

breaks down the epidermis and further excoriations enable access of pathogenic bacteria resulting in secondary infection [8–12]. Secondary bacterial infections may also result in abscess formation, cellulitis, joint and bone infections and sepsis. Pyoderma is a common complication of scabies, especially in patients with numerous lesions [11]. Skin infections may also lead to ARF [13] and other complications such as APSGN.

Whilst there have been two nephritogenic streptococcal antigens identified (pyrogenic exotoxin B and glyceraldehyde-3-phosphate dehydrogenase) in the pathogenesis of post-infectious glomerulonephritis in adults is more commonly associated with staphylococcal and other non-streptococcal infections [84].

13.4.3.2 Immune Complex-Mediated Nephritis

The immune complex mediated nephritis theory involves scabies mites or mite products together with specific antibodies forming immune complexes that cause glomerular injury. In a case report by Wang et al. [85] a potential mechanism of nephritis was proposed, namely that an immune complex including scabies mite or mite products may lead to immune complex mediated nephritis. Wang et al. [85] described deposition of complement, immunoglobulin and fibrin by immunofluorescence in the glomeruli. The authors proposed that the scabies mites and the bacterial superinfection may both be implicated in the development of acute nephritis.

13.5 Pathogenesis

13.5.1 Role of GAS

Specific nephritogenic strains of GAS are believed to predispose to immune complex disease causing glomerular inflammation and complement activation leading to APSGN.

There are several potential mechanisms proposed for the role of GAS in immunological glomerular injury [86]:

- Immune complex deposition (with streptococcal antigenic components)
- Molecular mimicry involving antibodies to streptococcal antigens cross-reacting to glomerular components
- Autoimmune reactivity: in specimens from renal biopsies in patients with acute PSGN, anti-IgG activity (in the eluate) was detected along with anti-IgG glomerular deposits [86]. It has been proposed that immunoglobulins may be modified by streptococcal neuraminidase, rendering them autoantigens [87].
- Animal studies propose the in situ formation of immune complexes, involving deposition of nephritogenic streptococcal antigens within the glomerulus [86, 88].

13.5.2 Bacterial Strain Specificity

In a study of patients based in Trinidad [63] investigated acute rheumatic fever or acute glomerulonephritis during an outbreak of scabies and impetigo (secondary) and reported that streptococcal strains colonising the skin in patients with impetigo were different from those associated with acute rheumatic fever. Although Groups G and C streptococci have been commonly identified in the throat of Indigenous people, they have not so commonly been identified in pyoderma lesions [64].

13.5.3 Streptococcal Serotypes Associated with Epidemics

Reid et al. [89] reported on monitoring of all cases of APSGN in 1986 in response to the rising incidence of scabies in Trinidad from 24.2 to 59.5 per 100,000 in 1985. From the 181 cases of APSGN; there was a bimodal distribution of isolates with the Streptococci M type in the March–May phase in 20% of the isolates serotyped. The Streptococci M type 48 was isolated in 4% and preceded first phase of the epidemic. Provisional type 5757 was isolated in seven patients (six from skin lesions, one throat) and was associated with 14% of the strains. The July–October second phase was associated with the nephritogenic M-type 55 serotype [89].

13.5.4 Investigations and Diagnosis

When a diagnosis of APSGN is suspected, a thorough skin examination is needed to look for any features of pruritis and secondarily infected scabies. Clinicians should carefully examine patients presenting with APSGN and a history of severe pruritis, as scabies can present atypically. In some patients, skin and renal biopsies may be indicated [85].

Conversely, where scabies and secondary GAS infection is common, routine testing of urine for albumin is essential to make an early diagnosis of APSGN. In addition, patients should also be examined for clinical signs of peripheral oedema, hypertension and cardiac failure.

13.5.5 Diagnosis of Scabies

Diagnosis of scabies is primarily through history and clinical examination. The diagnosis can be confirmed through detection of scabies mites, eggs or faeces on microscopic examination (scabies preparation), often through skin scrapings. However, a negative scabies preparation cannot rule out scabies. Dermoscopy can also assist in diagnosis.

13.5.5.1 Diagnosis of APSGN

APSGN may be suspected clinically with the patient presenting with cola-coloured urine, peripheral oedema and headaches caused by hypertension. Subsequent investigations should assess for acute renal dysfunction manifesting as proteinuria, microscopic haematuria, leucocytosis and hypoproteinaemia. A renal biopsy is generally not performed to confirm the diagnosis [90].

As the presentation of PSGN can vary from asymptomatic microscopic haematuria to acute nephritic syndrome (with hypertension, acute kidney injury, proteinuria, oedema and gross haematuria) it is important to assess for nephropathy in patients with scabies. This is particularly important in cases with suspected secondary GAS skin infections as a result of pruritus as ASPGN may further develop into chronic disease. Urinalysis may reveal red blood cell casts, dysmorphic red blood cells or proteinuria. Diagnosis of PSGN includes evidence of a recent GAS infection (through serological tests such as anti-streptolysin (ASO), skin culture or positive throat culture) and acute nephritis (haematuria ± red blood cell casts, variable degrees of proteinuria, oedema, oliguria and hypertension). Whilst a reduction in C3 levels can be useful in diagnosing PSGN, reductions in C3 can also be seen in other forms of glomerulonephritis (for example, membranoproliferative glomerulonephritis).

13.5.6 Management

13.5.6.1 Treatment of Scabies and Infection

Scabies

When diagnosed, first line treatment for scabies [29] involves topical permethrin 5% applied to the entire body (head to toe). Application should be repeated again 1 week after initial treatment as permethrin is not ovicidal and hatched mites need to be eradicated (Level of Evidence GRADE 1A). Topical permethrin is recommended in pregnancy. Household and intimate contacts should be examined and treatment offered to reduce the likelihood of ongoing infections in the household.

When permethrin fails, is contraindicated or in contexts of high prevalence when mass drug administration may be trialled [23], oral ivermectin (200 μg/kg by weight band dosing) given on day 1 and again 1 week later is recommended. Oral ivermectin should not be used in children less than 5 years of age or under 15 kg, and in pregnant or breastfeeding women (Level of Evidence GRADE 1A).

13.5.6.2 Treatment of GAS Secondary Infection of Scabies

Benzathine Penicillin G should be administered to patients with streptococcal infection if infection is still evident at time of APSGN diagnosis. Reports have suggested that if streptococcal infection treatment is initiated early, it may reduce the severity of prevent glomerulonephritis [91].

Patients who are penicillin allergic, or refuse IM Benzathine should as an alternative receive cotrimoxazole daily for 5 days, or twice daily for 3 days [92].

13.5.6.3 APSGN Management

The management of APSGN is focused on symptom control and managing the secondary complications including hypertension and fluid overload. Frusemide is commonly used, sodium restriction recommended and blood pressure managed with anti-hypertensives to prevent hypertensive encephalopathy. Very occasionally, dialysis may be required to manage uraemia, hyperkalaemia or fluid overload if refractory.

13.5.6.4 Community Screening and Mass Drug Administration for Scabies

There is evidence to suggest screening of children and family contacts within communities with endemic skin infections/infections ± intervention with IM penicillin may reduce burden of disease, control epidemics and possibly influence the development of nephritis. However, this requires extensive resources and is based on a couple of small studies [91, 93]. NT guidelines recommend when >2 cases of APSGN are diagnosed in the same month from the same community, screening of the children in the community should commence. APSGN is a notifiable condition in some states of Australia [94].

Mass drug administration has been investigated in multiple studies over recent decades as public health strategies for management of skin infections and scabies. The first of these was in 1986, with mass drug administration of permethrin in Panama which saw a drop in scabies prevalence from 33% to 1%, and GAS impetigo from 32% to 2% [26]. However, unfortunately due to the political turmoil in 1989, the prevalence rose again to 12% [26].

Similar studies have also been performed in the Northern Territory of Australia [18] within a remote Indigenous Community. With use of permethrin mass drug administration, the prevalence of scabies at 25 months decreased from 32% to 6% ($p < 0.001$) in children, and from 29% to 0% in adults ($p = 0.003$) in adults. Impetigo prevalence also reduced in children from 69% to 30% after 9 months ($p = 0.0002$). Kearns et al. [95] investigated scabies prevalence through population census with sequential MDAs of ivermectin 200 μg/kg repeated again after 2–3 weeks if scabies was diagnosed. It was reported that the scabies prevalence reduced 6 months after each MDA, with a low risk of acquisition (1%–2%) [95].

13.5.7 Strategies to Prevent Further Outbreaks of APSGN

Screening along with skin control measures (health promotion, environmental interventions and treatment) are likely to add additional benefit to current clinical treatments to achieve a sustained reduction in the prevalence of scabies and impetigo. Due to movement between households and communities, treatment of scabies is difficult as a result of the high reinfection rates [96].

PSGN arises in the same environments as RHD, is also caused by group A streptococci (GAS), and usually, as with RHD, is associated in remote-living Aboriginal populations with skin rather than throat infections. In a series of health screens in

one remote community in the Northern Territory of Australia, Hoy et al. (2021; unpublished data) have defined a strong relationship between RHD, and through PSGN, and renal disease. The most recent screen, which included medical record review, was performed from 2004 to 2006, and 1521 people, or more than 80% of the ambulatory, non-dialysis population of 5 years of age and older, participated. Among them, 51 (3.5%) had a documented history of acute rheumatic fever (ARF), 70 (4.6%) had a diagnosis of RHD and 165 (10.9%) had a history of PSGN, all of them in episodes at least 5 years prior to screening. As expected, the relationship of RHD to past episodes of ARF was very powerful, with an OR of 129 (95% CI 98–429), $P < 0.001$.

Histories of acute rheumatic fever and RHD were both significantly associated with histories of PSGN, with adjusted ORs of 2.23 (1.09–4.57), $p = 0.028$, and 2.12 (2.47 (1.39–4.38), $p = 0.02$ respectively. Unsurprisingly, ARF and RHD were significantly correlated with pathologic albuminuria. A history of RHD conferred an adjusted risk of ACR $\geq$ 3.4 of 2.14 (1.03–4.47), $p = 0.041$, and of ACR $\geq$ 34 of 2.0 (1.08–3.67), $p = 0.027$ respectively.

Hoy (2021) suggests that the therapeutic targets and that the development and efficacy of any intervention, including vigorous anti-scabies treatments and potential vaccines, be evaluated, on a community basis, against future vs. past episodes of endemic and epidemic PSGN, as well as rates of albuminuria and haematuria, and serum creatinine levels to derive estimates of excretory renal function. The broader use of Ivermectin against scabies holds great promise for reductions in both PSGN and RHD, especially if strategies against scabies reinfection are implemented and maintained.

Overall, studies have shown that mass drug administration for decreasing the burden of scabies and impetigo represents an effective strategy. However, the effectiveness is dependent on the community engagement and risk of re-introduction by neighbouring communities [50]. Mass drug administration is recommended in resource-limited communities where there is a high prevalence of scabies. However, this is dependent on the community being fully informed of the benefits and risks, being supportive of the initiative and also being given the opportunity to inform the planning, implantation and evaluation of the program.

13.5.7.1 Imperative to Prevent Childhood Illnesses That Result in Chronic Diseases That Are a Burden to Both the Patient and Healthcare System

Each year, over 163,000 people worldwide die from GAS sepsis [57]. Furthermore, complications from GAS can lead to APSGN and ARF, both of which can later result in chronic diseases with chronic kidney disease and chronic heart disease. Unfortunately due to environmental and primordial factors, in some communities, conditions such as impetigo, ARF and APGSN still exist, and further strategies are needed to prevent childhood illnesses resulting in chronic diseases. In Australia, chronic disease accounted for 90% of deaths in 2011 and is the number one cause of death, illness and disability [97].

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The International Alliance for the Control of Scabies (IACS)

14

Roderick Hay and Olivier Chosidow

While it is difficult to define the exact origins of this new focus on an old disease, scabies, it developed as a result of recognising a common interest amongst groups based in Australia, Europe, Africa, Latin America and the United States. For some time, scabies has been identified as an important health problem in disadvantaged communities, including indigenous population of Australia and the West Pacific [1]. The disease burden is not simply confined to the direct effects of parasitic infection itself, but also to the stigma and societal disruption caused by the disease, as well as its complications such as those related to secondary Group A Streptococcus and *Staphylococcus aureus* infections. These include impetigo, skin and soft tissue infection, sepsis and post-streptococcal glomerulonephritis and rheumatic fever [2, 3]. The problems posed by widespread and poorly controlled infection in the poorest communities had been highlighted over many years by the work of a group based in the Menzies School of Health Research in Darwin, Northern Territory, Australia. In addition, scientists from different countries have been working on the mechanisms by which secondary streptococcal infection interacts with the *S. scabiei* as well as mite biology [4]. Over a similar period, there had been an increasing awareness by dermatologists of the need to bring public health strategies to focus on infectious skin diseases such as scabies as well as the better publicised issues of skin cancer and occupational dermatoses [5, 6]. Subsequently, a group of dermatologists under the aegis of the International Foundation for Dermatology held a workshop that brought together dermatologists and public health experts in Atlanta in 2004. The aim of the meeting was to define targets amongst skin disease and infections in

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poor communities that might be amenable to control or elimination through simple and sustainable measures. As a result, scabies was identified as the most important target for this work as the tools for treatment were available and control was potentially achievable [7].

Representatives of these groups met in 2009 to discuss possible ways forward for collaboration and establishing a means for control, through Mass Drug Administration (MDA) or other measures, and as a result of this discussion, the decision was made to form a new Global body to promote and lead this work, subsequently called The International Alliance of the Control of scabies (IACS).

The aims of the Alliance are:

To advance the establishment of global control measures for reducing the impact of scabies on human populations.
To bring together professionals from a diverse experience in the international community with a common interest in scabies.
To publicise the adverse effects on human health caused by scabies and complications, promote scientific and medical interest in scabies and the benefits of control.
To provide a focus for determining and monitoring the global burden of human scabies.
To develop recommendations for diagnosis, management and community control.
To develop a research agenda based on priority scientific questions, creating a broad evidence base to inform a coordinated approach to control.
To work with relevant partners, including governmental as well as non-governmental bodies, to achieve these aims.
To ensure that measures developed by the alliance are adopted by national and international organisations, such as the World Health Organisation.

The last of these has proved to be a key step in the strategy for scabies, and after discussion, representatives of World Health Assembly member states (Ethiopia and Fiji) endorsed a proposal to the WHO Strategic and Technical Advisory Group (STAG) for recognition of scabies as a Neglected Tropical Disease (NTD). This status was approved in 2017. Since this time scabies has been recognised, along with other ectoparasitic infections, by the WHO as a Neglected Tropical Disease, and subsequent activities have devolved from this, including the recognition of ivermectin as an essential medicine approved by the WHO for public health control of scabies in 2019 and the convening of a regional WHO workshop to address key issues for scabies control and further work in Manila in 2019. Members of IACS play a key role in working with WHO and other International Agencies as well as Ministries of Health in affected areas to advise on and advocate for public health measures to combat scabies in endemic areas.

The other activities of IACS have also been important contributory factors in the goal to enlarge the scientific knowledge base and improve diagnostic, mapping and management strategies. As part of this, the organisation hosts an annual meeting which is usually held to coincide with the annual meeting of the American Society of

Tropical Medicine and Hygiene and the Coalition for Operational Research on Neglected Tropical Diseases (COR NTD) meeting, or on line. The annual meeting is a forum for presented papers, workshops and panel discussions. There have also been presentations and workshops organised by IACS members at key Tropical Medicine and NTD meetings such as COR-NTD in the United States and the European Congress on Tropical Medicine and International Health. IACS is a member of the Neglected Tropical Disease NGO Network (NNN) Skin NTD Cross Cutting group. These initiatives provide additional opportunities to work with the wider NTD and tropical infection communities and to continue the mission of advocacy through lobbying and writing. This is supported through IACS-promoted publications [8–10].

Key to this work has been the need to align work on scabies with current strategies for control and research on NTDs because of their common presentation on the skin, through adoption of an integrated approach to diagnosis, mapping, control, training and disability reduction provide economy of scale. The use of the designation, Skin NTD, was swiftly included in IACS strategy [11–13].

Improving diagnosis, particularly where this is needed in resource poor settings, has been a specific goal, and recently, the results of consensus diagnostic guidelines, which can be used in settings both with or without technical and laboratory facilities, were published by members of IACS [14, 15]. A further goal has been to establish criteria for deploying MDA in community treatment as a public health strategy. In 2018, the International League of Dermatological Societies and IACS submitted an application to the Essential Medicines Committee of the WHO in collaboration with the department of Neglected Tropical Diseases for recognition of ivermectin as an Essential Medicine for the community control of scabies. This was approved by the World Health assembly in 2019, and it provides support for the use of ivermectin in control programmes based on mass drug administration.

IACS welcomes the participation of the wider community of scientists and clinicians already working in the field as well as new members. The mission statement of IACS, which can be accessed on the web site www.controlscabies.org, provides the context: The International Alliance for the Control of Scabies (IACS) is a global network committed to the control of human scabies and the promotion of health and well-being of all those living in affected communities.

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Part IV

Clinical Manifestations and Management

Common Scabies and Special Presentations

15

Sarah J. Coates, Cristina Thomas, and Aileen Y. Chang

15.1 Clinical Features of Common Scabies

15.1.1 Pruritus

A characteristic feature of common scabies is generalized pruritus, often worse at night. Pruritus most commonly localizes to associated skin lesions, as described below, but can also occur in uninvolved skin. Severe pruritus worsens quality of life in children and adults [1–3].

Pruritus may be absent or minimal in infants [4], the elderly [5], those with cognitive impairment [5], patients with immunosuppressive medical conditions [6], those treated erroneously with topical corticosteroids [7, 8], or those taking immunosuppressive/anti-inflammatory agents [9]. Early in infestation, pruritus may be absent because host sensitization to mite antigens occurs only 4–6 weeks after the initial infestation [10]. However, with reinfestation, symptoms present within days.

Pruritus is likely due to nonhistaminergic itch mediators, including tryptase, its receptor PAR-2, and ion channels TRPV1 and TRPA1 [11]. As such, scabies pruritus does not respond well to therapy with antihistamines. Importantly, pruritus is an adverse effect of several topical antiscabietic agents, including permethrin 5% cream, benzyl

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benzoate 10%–25% lotion, malathion 0.5% lotion or aqueous liquid, and crotamiton 10% cream or lotion [12]. The 2020 International Alliance for the Control of Scabies (IACS) consensus criteria for scabies-related pruritus include (1) generalized or localized pruritus, (2) signs of excoriations and behaviors including scratching affected areas, particularly in children, (3) itch that is not considered to be more likely the result of another cause (e.g., localized to visible arthropod bites), or more than one of these [13].

Even after appropriate treatment, pruritus may persist for up to 4 weeks and does not necessarily indicate treatment failure [14]. Rather, postscabietic pruritus is thought to represent the host hypersensitivity response that abates with time.

15.1.2 Typical Lesions

Scabies presents with multiple morphologies, and the differential diagnosis varies by clinical subtype (Table 15.1).

In common scabies, in the absence of highly specific signs such as burrows or male genital lesions, determining whether or not skin lesions are typical for scabies is based upon consideration of both *morphology* and *number*. The *morphology* of a typical scabies lesion is a small, elevated, easily palpated lesion, usually a papule

Table 15.1 Differential diagnosis of scabies

Common scabies	Arthropod bites
	Folliculitis
	Impetigo
	Papular urticaria
	Atopic dermatitis
	Contact dermatitis
	Nummular eczema
	Prurigo nodularis
	Bullous pemphigoid (urticarial stage)
	Dermatitis herpetiformis
	Lice infestation
	Delusional parasitosis
Nodular scabies	*Infants*
	Mastocytosis
	Langerhans cell histiocytosis
	Indeterminate cell histiocytosis
	Urticaria pigmentosa
	Cutaneous pseudolymphoma
	Adults
	Cutaneous pseudolymphoma
	Cutaneous histiocytosis
	Cutaneous B cell lymphoma
Bullous scabies	Bullous arthropod bites
	Bullous impetigo
	Bullous pemphigoid
	Pemphigus vulgaris
	Incontinentia pigmenti (inflammatory stage)

2–3 mm in diameter (Figs. 15.1 and 15.2) [13]. Larger nodules, typically 5–10 mm in diameter, can be considered typical lesions when they occur in particular locations (see Sect. 15.2.2). Lesions are usually erythematous (pink to red) but may be

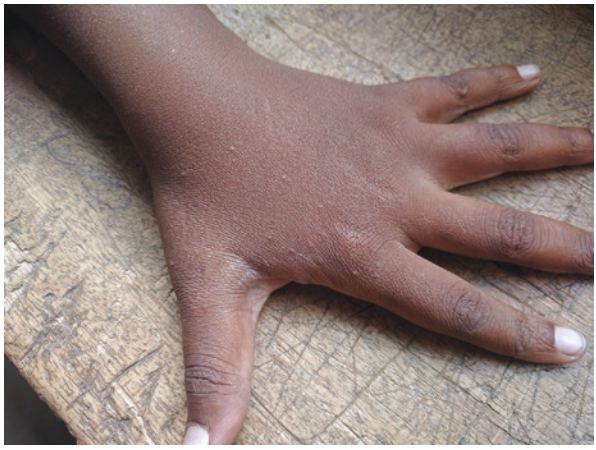

Fig. 15.1 Papules and scaling on the dorsal hand and interdigital webspaces. (Courtesy of Dr. Aileen Chang)

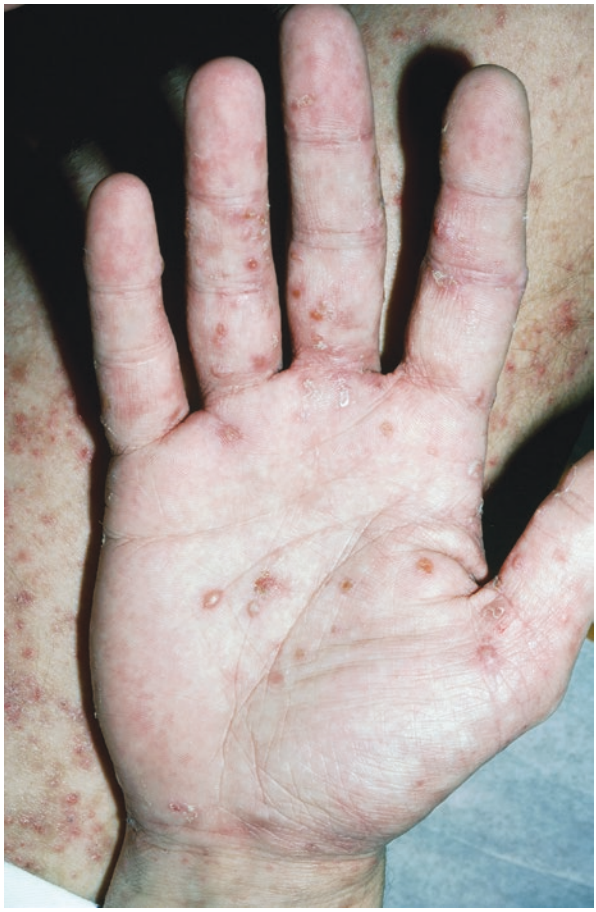

Fig. 15.2 Excoriated papules and scaling on the palm and fingers. (Courtesy of Dr. Timothy Berger)

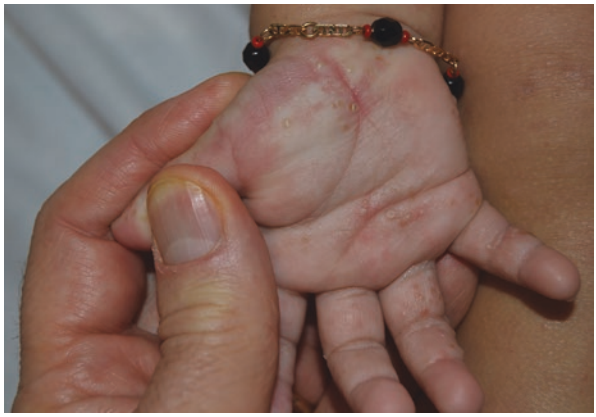

Fig. 15.3 Vesicles and pustules on the palm and fingers in an infant. (Courtesy of Dr. Scott Norton)

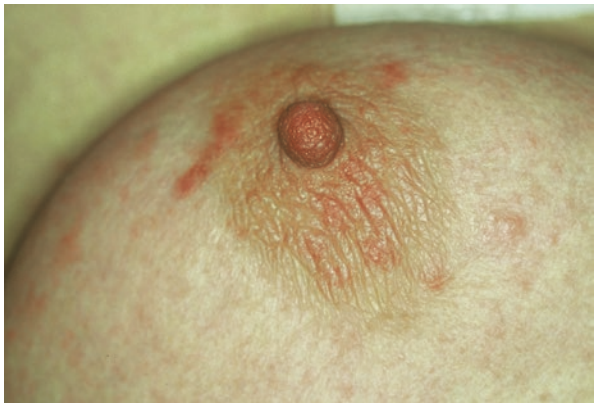

Fig. 15.4 Erythematous papules over the nipple and areola. (Reproduced from *The New England Journal of Medicine*, Olivier Chosidow, Clinical Practice. Scabies, Vol. 354, Pages 1718–1727, Copyright 2006 Massachusetts Medical Society. Reprinted with permission)

hyperpigmented in darker-skinned individuals [13]. Vesicles and pustules are less commonly seen in adults than in infants (Fig. 15.3) [13]. In terms of *number*, to be classified as typical, there should be at least three lesions on the same body area, or within an area of approximately 10–20 cm diameter [13]. Typical lesions favor the finger webspaces, hands, volar wrists, axillae, feet, waistline, lower buttocks, inner thighs, areola in women (Fig. 15.4), and genitalia in men [12].

15.1.3 Burrows

Burrows, which represent tracks created by a fertilized female scabies mite tunneling through the stratum corneum, are a highly specific finding (Fig. 15.5) [13]. Although considered highly specific for scabies, burrows are only occasionally visible in common scabies, in which the average mite load is 5–15 [15]. Burrows appear as short (3–7 mm), linear, or wavy tracks ending in an erosion or intact vesicle/pustule containing a mite [12]. The superficial end, representing the original entry point of the mite, may be scaly and easier to see with the naked eye. Occasionally, this point may appear as a "V" shape that is described as the "wake sign" [13]. The morphology of burrows may be altered by excoriations and secondary bacterial infection [13]. Burrows are typically found on the

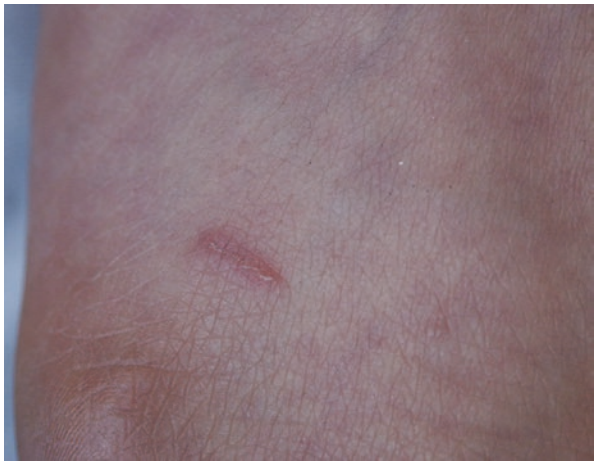

Fig. 15.5 Typical linear burrow ending in a pinpoint vesicle. (Reproduced from *The New England Journal of Medicine*, Olivier Chosidow, Clinical Practice. Scabies, Vol. 354, Pages 1718–1727, © 2006 Massachusetts Medical Society. Reprinted with permission)

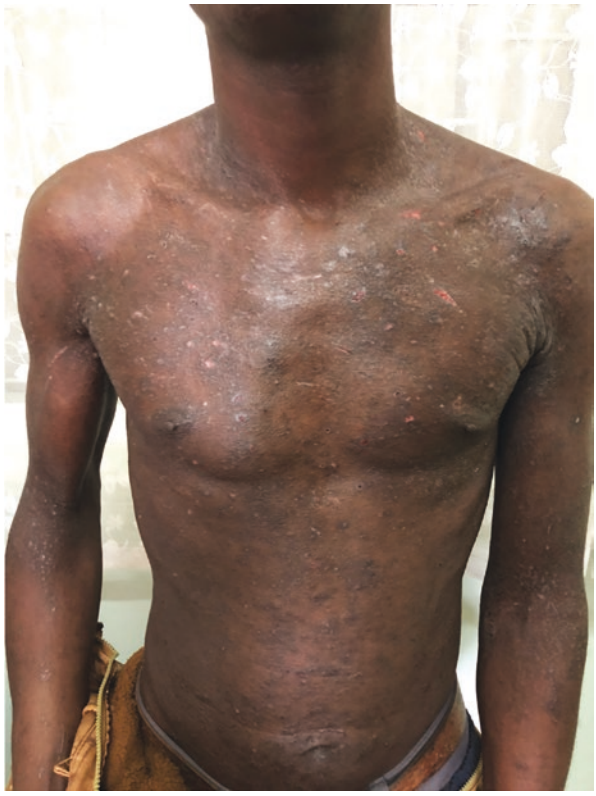

Fig. 15.6 Diffuse linear excoriations, excoriated papules and eczematous plaques in a patient with scabies. (Courtesy of Dr. Sarah Coates)

hands and flexural wrists, but may also occur on the elbows, genitalia, buttocks, and axillae. More common than burrows, the typical lesions described above or nonspecific secondary lesions, such as excoriated papules and eczematous plaques, are seen (Fig. 15.6). Signs of prolonged scratching, including secondary impetiginization (Fig. 15.7), lichenification, and prurigo nodularis, may also be present.

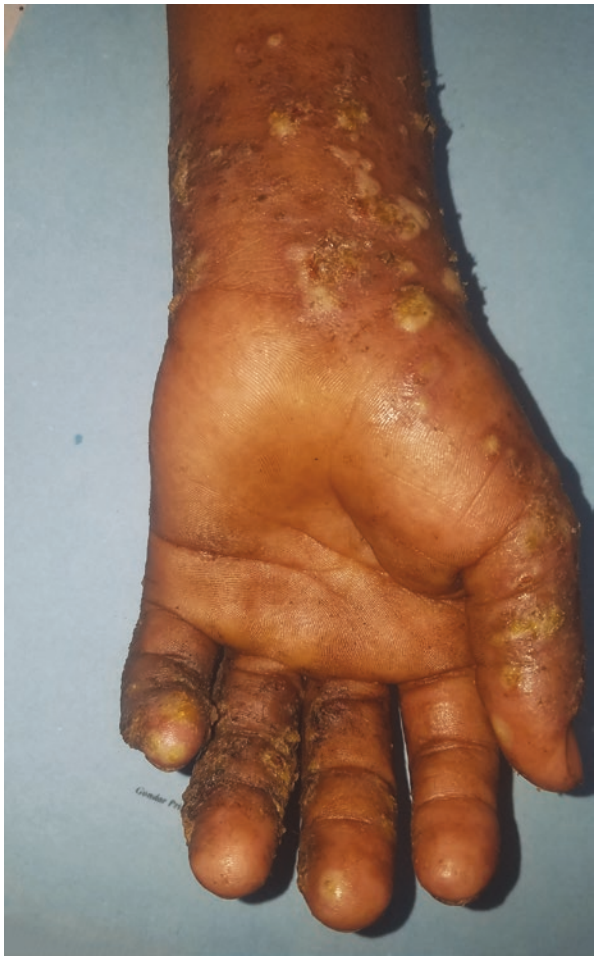

Fig. 15.7 Impetiginized scabies with pustules and plaques with honey-colored crust on the ventral wrist and palm. (Courtesy of Dr. Wendemagegen Enbiale)

15.1.4 Historical Features

In common scabies, mite transmission is most frequently due to prolonged skin-to-skin contact, including sexual contact. According to the 2020 IACS criteria (Table 15.2), close contacts are defined as any of the following: individuals that sleep in the same dwelling, individuals that share a bed (including sexual partners), children in the same classroom or who play closely together, and adults with known skin-to-skin contact, e.g., through occupational exposures (healthcare workers, residential care workers, caregivers, and educators of children) and recreational exposures (e.g., contact sports such as wrestling) [13].

Table 15.2 The 2020 International Alliance for the Control of Scabies Consensus Criteria for the Diagnosis of Scabies [13]

A. Confirmed scabies
At least one of:
A1: Mites, eggs, or feces on light microscopy of skin samples
A2: Mites, eggs, or feces visualized on individual using high-powered imaging device
A3: Mite visualized on individual using dermoscopy
B. Clinical scabies
At least one of:
B1: Scabies burrows
B2: Typical lesions affecting male genitalia
B3: Typical lesions in a typical distribution and two history features
C. Suspected scabies
One of:
C1: Typical lesions in a typical distribution and one history feature
C2: Atypical lesions or atypical distribution and two history features
History features
H1: Itch
H2: Positive contact history
All of the following are considered high risk for scabies transmission:
Any contact with an individual diagnosed with crusted scabies
Close contact with an individual diagnosed with scabies
Close contact with an individual with itch not accounted for by another condition
Close contact with an individual with typical scabies lesions in a typical distribution that are not accounted for by another condition
Close contacts are defined as any of:
1. Individuals that sleep in the same dwelling
2. Individuals that share a bed (including sexual partners)
3. Children in the same classroom or who play closely together
4. Adults with known skin-to-skin contact, e.g., through occupational exposures (healthcare workers, residential care workers, caregivers, and educators of children) and recreational exposures (e.g., contact sports such as wrestling)
Notes:
1. *Diagnosis can be made at one of the three levels (A, B, or C)*
2. *A diagnosis of clinical and suspected scabies should only be made if other differential diagnoses are considered less likely than scabies.*

15.1.5 Applying the IACS Diagnostic Criteria

The 2020 IACS diagnostic criteria (Table 15.2) recommend using a combination of microscopic findings, clinical findings, and history features when rendering a scabies diagnosis. Historical features include itch and a positive contact history, as defined above. While the presence of mites on microscopic or visual exam can be used alone to establish a diagnosis, given the low mite burden in common scabies,

clinical criteria are often heavily relied upon in both resource-poor and resource-replete settings because of the low mite burden in common scabies. Any one of the following clinical criteria is sufficient for a "clinical scabies" diagnosis: (1) scabies burrows, (2) typical lesions affecting male genitalia, or (3) typical lesions in a typical distribution and two history features. A "suspected scabies" diagnosis can be made based on either (1) typical lesions in a typical distribution with one history feature, or (2) atypical lesions or an atypical distribution with two history features [13].

15.2 Atypical Presentations of Scabies

According to the 2020 IACS diagnostic criteria, lesions without typical morphology, or those that number fewer than three in any body area, are classified as atypical [13]. Additional atypical findings in patients with scabies infestations may include scalp involvement, nodules, or bullous lesions.

15.2.1 Scalp Involvement

Scalp involvement in scabies is rare in healthy adults, and in fact, diffuse pruritus in the absence of any involvement from the neck up warrants a thorough evaluation for possible scabies infestation. Scalp involvement by scabies most frequently occurs in infants, children, the elderly, and immuno compromised individuals [4, 16, 17].

15.2.2 Nodular Scabies

Nodular scabies presents with firm, red-brown, or violaceous nodules, typically 5–10 mm in diameter, and most commonly located in the axillae, groin, male genitalia, and trunk (in infants) (Figs. 15.8 and 15.9) [18]. This form of scabies occurs in approximately 7% of cases in the pediatric and young adult population [19].

In infants, nodular scabies may mimic infantile mastocytosis [20], urticaria pigmentosa [21], Langerhans cell histiocytosis [22], or indeterminate cell histiocytosis [23]. In adults, it may mimic cutaneous histiocytosis or pseudolymphoma (Table 15.1).

There are at least two theories of scabietic nodule pathogenesis. These lesions were previously thought to constitute a delayed-type hypersensitivity reaction to mite antigens, and were thus categorized as a type of cutaneous pseudolymphoma, similar to those that occur following an arthropod bite [24]. Therefore, it was thought that scabietic nodules do not contain mite elements. Another theory suggests that nodules develop as a result of deeply penetrating mites that are missed on skin scrapings or routine sectioning of skin biopsies. In one study, 22% of scabietic nodules contained mite parts on histopathologic examination [25]. Furthermore, an additional case series [26] and individual case reports [27, 28] have identified intact

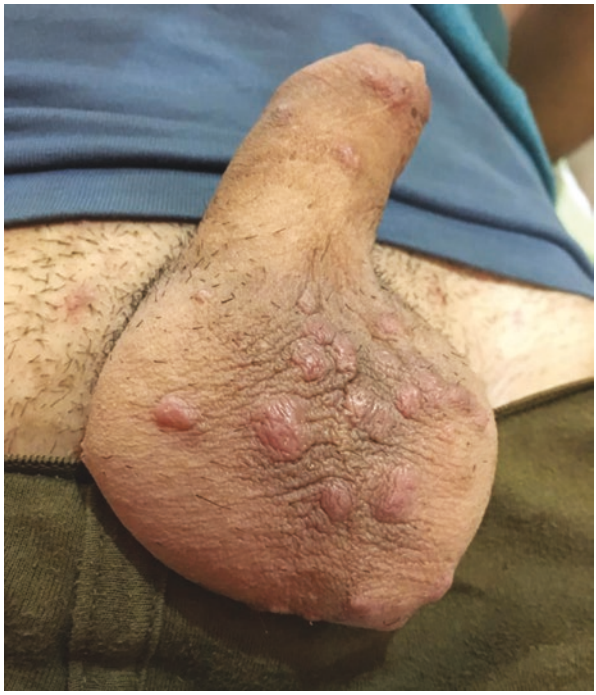

Fig. 15.8 Nodular scabies in an adult male with pink nodules on the scrotum and penile shaft. (Courtesy of Dr. MP Ashraf)

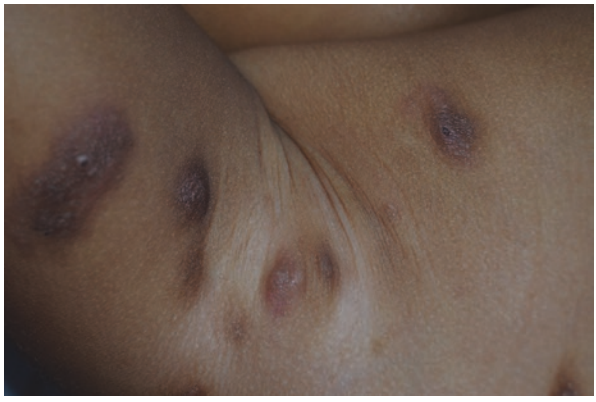

Fig. 15.9 Nodular scabies in an infant with erythematous and hyperpigmented nodules in the axilla. (Courtesy of Dr. Scott Norton)

scabies mites within scabietic nodules, suggesting that in at least some cases, active infestation drives nodule development.

Patients with nodular scabies should be treated with standard antiscabietic treatment, with the choice of oral versus topical determined by the overall disease burden rather than the presence of nodules per se. However, providers should be aware that nodular lesions often persist for months despite appropriate treatment. For patients with persistent nodules despite completion of an appropriate antiscabietic treatment course, topical corticosteroids, topical calcineurin inhibitors [29], and

intralesional corticosteroids [30] have all been used successfully to treat prolonged hypersensitivity reactions.

15.2.3 Bullous Scabies

Bullous scabies is characterized by tense or flaccid bullae in a typical distribution with or without associated itch. The pathogenesis of bullae formation during scabies infestation is unknown, but may include (1) autoantibody-mediated bulla formation due to basement membrane antigen disruption by the scabies mite [31–33], or alternatively, a component of the mite itself cross reacting with the bullous pemphigoid (BP) antigen (antigenic mimicry) [32]; (2) bullous impetigo due to coinfection with *Staphylococcus aureus* [6, 32]; or (3) an autoeczematization (id) reaction to the scabies mite [34].

The differential diagnosis for bullous scabies includes autoimmune blistering disorders, bullous arthropod bites, and bullous impetigo (Table 15.1). Importantly, misdiagnosis of autoimmune bullous disorders in the setting of scabies infestation may result in unnecessary exposure to potentially harmful immunosuppressive medications [35].

Bullous scabies may especially be mistaken for BP due to shared clinical and histopathologic features [32, 36–39]. This is particularly relevant in elderly populations, who are most at-risk for BP and who are also more likely to have atypical scabies presentations. Both BP and scabies may display abundant eosinophils on skin biopsy and, importantly, the urticarial phase of BP may lack a subepidermal split, further contributing to diagnostic confusion [37]. Since mite burden is low in common scabies, the absence of mite, ova, or feces identification cannot be relied upon to rule out a diagnosis of scabies [40]. In the absence of identifiable mites, ova, or feces when bullous scabies is suspected, direct (DIF) and indirect immunofluorescence (IIF) should be obtained, and characteristic findings of autoimmune bullous disease identified, before rendering a diagnosis of BP. Importantly, basement membrane deposition of immunoglobulins, including IgG, and C3 on direct immunofluorescence has been reported in numerous patients with scabies [32, 37–39, 41, 42]. In fact, as above, some have postulated that the presence of the scabies mite, or its secretions, may alter or release the BP antigen from the basement membrane, initiating an immunological response. Given the high overall prevalence of positive DIF in the setting of bullous scabies, IIF for BP180 and BP230, the target antigens in BP, may be more helpful, as it is typically negative in scabies [39]. Negative enzyme-linked immunosorbent assay (ELISA) testing has also been reported to be helpful in distinguishing scabies from BP [43]. In nuanced cases, peripheral blood eosinophilia and elevated IgE are generally not helpful, because these laboratory findings can be observed in both scabies and bullous pemphigoid [44–46].

Of note, positive IIF occurring in the aftermath of scabies infestation has been suggested as evidence for a scabies-induced mechanism in the multifactorial pathogenesis of BP [33]. Indeed, in a population-based study in Taiwan, the hazard ratio for developing BP following scabies infestation was found to 5.93 (95% confidence

interval 3.26–10.78) [47]. Physicians caring for patients, especially elderly patients, with a recent history of scabies should therefore be cognizant of the potential for subsequent BP development.

Bullous scabies has also been mistaken for other blistering disorders, such as acquired epidermolysis bullosa [48] and dermatitis herpetiformis [49]. Of note, patients with underlying coagulopathies may present with hemorrhagic bullae as primary lesions [50].

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Scabies Itch

16

Hei Sung Kim and Gil Yosipovitch

16.1 Scabies Itch: The Clinical Features

16.1.1 The Properties of Scabies Itch

The key symptom of scabies is extreme, incessant itch that is profound at nighttime [1, 2]. Shin and colleagues assessed scabies itch (n = 82) with a questionnaire to identify an itch severity of 7.2 ± 2.0 and an associated sleep interference of 6.8 ± 2.4 on a visual analog scale (VAS) [3]. The genitalia (62.2%), trunk (51.2%), and armpits (48.8%) were commonly affected, and the itch was mainly stinging (73%), burning (65.3%), and crawling (61.3%). The mean duration of itch before proper diagnosis was 3.0 ± 2.7 months in the study patients indicating significant diagnostic delay.

Strikingly, scabies patients present with a significantly higher number of scratch lesions compared to those with comparable itchy dermatosis (i.e., atopic dermatitis, nonatopic eczema, and urticaria) and are often unable to hold back from scratching during consultation [4–6].

The nocturnal itch in scabies is due to the mites' enhanced action at nighttime [7]. Their vigorous motion results in alloknesis/hyperknesis. Also, the fecal byproducts (i.e., scybala) contribute to itch [8].

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16.1.2 The Prevalence of Scabies Itch

Itch exists in nearly all classic scabies cases. The prevalence of itch is known to be lower in children and individuals with crusted scabies, an outcome influenced by the unique properties of these groups (i.e., reduced cutaneous sensation, inability to scratch, or convey itch) [9–14].

16.1.3 Consequences of Scabies Itch

Scabies itch can lead to grave consequences. Excoriations from incessant scratching promote skin entry of *Staphylococcus aureus* (*S. aureus*) and Group A streptococcus (GAS) which are infamously associated with a variety of local (e.g., skin and soft tissue infection, secondary impetigo, abscesses) and general complications (e.g., acute rheumatic fever, bacteremia, acute poststreptococcal glomerulonephritis, and rheumatic heart disease) [15–21].

16.2 The Suggested Pathophysiology of Scabies Itch

Itch is classified into two subtypes based on the neural pathways: histaminergic (in acute itch), and nonhistaminergic (mainly chronic itch) [22–24]. Sanders et al. have discovered significant increase of nonhistaminergic receptors such as protease-activated receptor (PAR-2), transient receptor potential vanilloid subtype 1 (TRPV1), and transient receptor potential ankyrin 1 (TRPA1) in the epidermis and tryptase+ mast cells in the dermoepidermal junction while failing to find histamine+ mast cells in scabies-infested skin which implies that itch in scabies is largely non-histaminergic [25]. The itch is likely the result of a complex interaction between the nervous system, cutaneous immune system, and keratinocytes (KCs) [23].

16.2.1 Host–Mite Interaction Which Possibly Contributes to Scabies Itch

Scabies itch is a combination of type I (immediate) and type IV (delayed) hypersensitivity response and encompasses both scabies mite activity and the host response toward the mite (Table 16.1) [8, 24].

A family of scabies mite gut proteins are linked to house dust mites (HDM) group 3 allergen [70]. Among them, Sar s 3, a serine protease, helps digest skin proteins and dissolves the epidermal barrier [71, 72]. Sar s 3 may cause itch by activating PAR-2 on various cell types (i.e., KCs, neurons, and mast cells) [27, 32, 33]. Proteolytically dormant serine protease paralogs (SMIPP-Ss) and serine protease inhibitors (Scabies Mite Serpins, SMSs) are reported to promote survival of GAS and *S. aureus* by interfering with the host complement cascade which may accentuate itch [34–38, 48, 72].

Table 16.1 The suggested pathophysiology of scabies itch

Host–mite interaction and secondary bacterial infection possibly contributing to scabies itch	
Direct scabies mite action	
Scabies Protease (Sar s 3, Sar s 1 a–e)	Activates **PAR-2 and MRGPRX2** on **Mast cells** and **Sensory neurons** → Evokes itch [27–31]
	Interacts with **PAR-2** on **KC**s [27, 32, 33]
Scabies Pseudoproteases (SMIPP-Ss, SMSs)	Impede host complement cascade → Help *S. aureus* and *S. pyogenes* survive [34–38]
Scabies mite	Interacts with TLRs on Sensory neurons → Evokes itch [39–41]
	Engages with TLR on various epithelial and immune cells (i.e., KCs, Mast cells, eosinophils, neutrophils, macrophages, dendritic cells) [24, 42–44]
	Triggers the complement system (i.e., C3a, C5a) [45, 46]
	HDM allergen protein homologs → IgE mediated Mast cell activation [47]
Secondary bacterial infection	
S. aureus δ-toxin	Activates **Mast cells** via **MRGPRX2** [48–50]
***S. aureus* Protease**	Activates **KCs** via **PAR-2** [51]
S. aureus and *S. pyogenes*	*S. aureus* activates KCs via TLR2 [48, 52, 53]
	Sensory neurons recognize *N*-formylated peptides and α-hemolysin from *S. aureus* and streptolysin S from *S. pyogenes* [54, 55]
Host response	
Complement system activation	C3a and C5a → Activate **Mast cells** to release mediators (i.e., **tryptase**, histamine, IL-31) [24]
KC activation	Via **PAR-2** and TLR → **Protease**, **AMP** (i.e., **β-defensin**), and cytokine (i.e., TSLP, IL-33) release → Activates **PAR-2** and **MRGPRX2** on **Mast cells and Sensory nerves,** and potentiates other host innate and adaptive immunity [25, 28, 30, 56–59]
	TSLP promotes periostin secretion from fibroblasts → Activates M2 macrophages [60]
Sensory nerve activation	Release of **Substance P** → Activates **MRGPRX2** and **NK1R** on **Mast cells** [26]
	Propagation of itch signals
Mast cell activation	**(Major)** Via **MRGPRX2** and **PAR-2** → Release of **nonhistaminergic pruritogens** (i.e., **tryptase**, IL-31) → **Sensory neuron** activation via **MRGPRX2, PAR-2** and IL-31R [49, 61–64]
	(Minor) Via IgE receptor → Release of histamine → Activation of Sensory neuron via H1, 4R [65]
Eosinophil infiltrates	Eosinophil granule proteins (i.e., MBP, ECP) release → Stimulates **MRGPRX2** on **Mast cells** [66]
	Release IL-4, IL-13 → Increased responsiveness of Sensory neurons to itch mediators [67]
Macrophage	Arginase-1 (+)/CD163 (+) M2 macrophages produce IL-31 → Elicit itch through IL-31R on Sensory neurons [60]

(continued)

Table 16.1 (continued)

Host–mite interaction and secondary bacterial infection possibly contributing to scabies itch	
Th1 response (classic scabies)	IFN-γ and IL-2 → Interact with TRP channels on Sensory neurons [68]
Th2 response (crusted scabies)	IL-4, IL-13 → Induce IgE production from B cells → Mast cell activation via IgE receptor [65, 67]
	IL-31 → Transmits itch by binding to IL-31R on Sensory neurons [58, 69]

Adopted from Ref. [26]

S. scabiei also produces five cysteine proteases (i.e., Sar s 1 a–e) similar to HDM group 1 allergen which likely cause itch via PAR-2 activation [28, 29, 72, 73].

Upon injury, KCs release proteases, antimicrobial peptides (AMPs), and cytokines that stimulate immune cells and nerve endings [74]. PARs on immune cells and neurons transmit itch [25, 56, 57]. β-defensin triggers the release of IL-31 by Th2 and mast cells which promote itch by working on sensory nerves [58, 69].

He et al. reported upregulation of the Toll-like receptor (TLR)-associated genes in scabies-infested hosts [47]. *S. scabiei* can provoke itch via TLRs-3, 4, 7 on sensory nerve endings which coexpress TRPV1 [39–41, 75]. KCs are able to identify *S. scabiei* and release alarmins, IL-33, or thymic stromal lymphopoietin (TSLP) which enhance host immune response [42–44, 59, 76]. TSLP sparks itch by its interaction with TRPA1 sensory neurons [76].

The complement system plays a central role in innate immunity and has been documented in scabies-infested skin [45, 46]. C3a and C5a activate mast cells to release mediators (e.g., tryptase, histamine) which cause itch [24].

Innate immune cells also react to *S. scabiei* infestation [24]. Eosinophils produce IL-4 and IL-13 (Th2 cytokines) which increase the responsiveness of sensory neurons to itch mediators, and eosinophilic granule proteins (i.e., major basic protein (MBP), eosinophilic cationic protein (ECP)) that activate mast cells [66, 67, 77].

Upon activation via TLRs, mast cells produce Th2 cytokines. By liberating histamine, substance P (SP), prostaglandins (PGs), tryptase, and leukotrienes (LTs), mast cells mediate allergic (IgE) response to *S. scabiei* [78–80].

Heavy infiltration of Arginase-1 (+)/CD163 (+) M2 macrophages were seen in classic scabies cases [60]. Scabies mite proteases are known to spark epidermal KCs to release TSLP, which subsequently boosts fibroblasts to secrete periostin. The protease–TSLP–periostin axis is believed as the key for M2 macrophages to produce IL-31 [60].

S. scabiei-infested skin has plenty of $CD4^+$ (Th1, Th2) and $CD8^+$ T cells which drive an inflammatory response [24]. IFN-γ and IL-2 (Th1 cytokines) are influential in ordinary scabies, whereas IL-4 and IL-13 are major cytokines found in crusted scabies patients [67, 68].

Mas-related G protein-coupled receptors (Mrgprs) have gained much attention in the field of non histaminergic itch [49, 61, 77, 81, 82]. Since proteases target Mrgprs, it is assumed that Mrgprs on mast cells and nerve endings (i.e., MRGPRX2) take part in scabies itch [30, 31, 81]. Substance P too activates MRGPRX2 on mast cells,

and the resultant liberation of non histaminergic itch mediators such as tryptase and IL-31 creates a ferocious cycle of itch [49, 61–64, 69].

16.2.2 Secondary Microbial Infection Which Likely Contributes to Scabies Itch

One potential mechanism of *S. aureus*-related itch is δ-toxin and serine protease [50, 51]. In addition, *S. aureus* communicates with TLR2 on KCs [52, 53].

N-formylated peptides and α-hemolysin from *S. aureus,* and streptolysin S from *S. pyogenes* transmit pain by directly acting on the nerve [54, 55]. Pruriceptors likely recognize these pathogens eliciting itch.

16.2.3 Sensitization: Possible Contribution to Scabies Itch

Peripheral sensitization with a reduced tolerance, heightened receptivity, and continuity is observed in chronic itch state [27]. Scabies infestation can ultimately potentiate nerve sensitivity to pruritic substances [8]. For example, PAR-2 activation led to non histaminergic nerve sensitization and itch in mice [83].

16.3 Scabies Itch Management

16.3.1 Treatment Directed on Scabies Mite

Since scabies mite (plus scybala and eggs) are the main cause of scabies itch, their elimination is the key to reduce itch [19].

As scabicides are explored in another chapter, we will just take time to mention briefly of the antipruritic effect of 10% crotamiton. It suppresses both histamine and chloroquine itch pathways and has been shown to alleviate scratching in mice [84].

Scabicides alone are usually insufficient in controlling scabies itch which persist for weeks even after a successful treatment. Anti-itch measures are a must while using scabicides as mass release of antigens and proteases from mite destruction can aggravate itch [85, 86].

16.3.2 Scabies Itch Control

Antihistamines are most often the choice for scabies itch, yet they have limited efficacy and mainly work by making patients sleepy and forget their itch [87].

PAR-2 takes part in scabies itch making it a good treatment target (Table 16.2) [25]. Recently, selective PAR-2 inhibitor (i.e., methylbenzyl methylbenzimidazole piperidinyl methanone (MMP)) creams have been tested and may be used to control scabies itch [88].

Table 16.2 Novel targets/options for scabies itch (Adopted from Reference [26])

Novel target	Therapeutic option
PAR-2	Cream with methylbenzyl methylbenzimidazole piperidinyl methanone (MMP) [88]
	Doxycycline and minocycline [87, 89]
	Polidocanol [1, 90]
	Emollient containing *Aquaphilus dolomiae* (ADE-G1) extract [91, 92]
MRGPRX2	Novel MRGPRX2 targeting antagonists [93, 94]
	Natural polyphenolic compounds (i.e., genistein, resveratrol) [95, 96]
	Shikonin [97]
	A tripeptide NK-1R antagonist (i.e., QSF) with dual activity on MRGPRX2 [98, 99]
Th2 cytokines	Biologics (i.e., anti-IL-33 monoclonal antibody (mAb), anti-Il-4α mAb, anti-IL-13 mAb, anti-IL-31 mAB and anti-IgE mAb) [22]
	New generation small molecule (i.e., Janus Kinase (JAK)) inhibitors [100, 105]
TRP channels	TRP channel modulators (e.g., topical capsaicin, topical calcineurin inhibitors, topical camphor, topical menthol, topical strontium hydrogel formulation (TriCalm™), and botulinum toxin) [101–103]

Notably, doxycycline and minocycline too have PAR-2 inhibitory properties and may be used for scabies itch [87, 89].

Polidocanol is a topical anesthetic which is thought to be a PAR-2 antagonist [1]. Over-the-counter polidocanol skin care products (e.g., Eucerin Dermo Capillaire™, Beisersdorf AG; Ducray Sensinol™, Laboratoires Pierre-Fabre) are available [1, 90].

MRGPRX2 (found on nonhistaminergic neurons and mast cells) may be a possible target of scabies itch (Table 16.2) [93, 94]. Newly found MRGPRX2 inhibitors include natural polyphenolic compounds and shikonin [95–97]. A tripeptide NK-1R antagonist (i.e., QWF) with dual activity on MRGPRX2 also seems to be a promising choice for scabies itch [98, 99].

Since type 2 inflammation (i.e., initiators IL-33 and TSLP, effector cytokines IL-4, IL-13, IL-31, and IgE) plays an important role in scabies itch, biologic agents and new generation small molecule (i.e., Janus kinase (JAK)) inhibitors may work for scabies (Table 16.2) [22, 100, 104, 105].

Transient receptor potential (TRP) channels transmit scabies itch and drugs which act on TRP channels (e.g., topical capsaicin, topical menthol, topical calcineurin inhibitors, topical strontium hydrogel formulation (TriCalm™), topical camphor, and botulinum toxin) have shown various degrees of success in scabies itch (Table 16.2) [22, 101–103].

Since superimposed bacterial infection from *S. aureus* and *S. pyogenes* further potentiates scabies itch, antibiotics should be delivered in suspected cases [106, 107].

16.3.3 Proposed Measures for Refractory Itch

If itching persists even with scabies directed treatment and anti-itch measures, one should consider treatment failure, scabicides-related skin irritation/explosive immune response, or delusion of parasitosis [108]. If a skin scarping with mineral

oil reveals mites, scabicides should be further applied [109]. In cases of significant skin inflammation, brief use of systemic steroids may be helpful. Antipsychotics (i.e., pimozide) are required for patients with delusion [110].

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Clinical Manifestations of Severe Scabies

17

Dana Slape, Rhiannon Russell, and Erin McMeniman

17.1 Introduction to Terminology

Severe scabies is the overarching term that covers crusted scabies as well as profuse and diffuse presentations of classic scabies. Classic scabies favours sites such as the acral webspaces, genitals and periumbilical areas and is initiated by an invasion of the stratum corneum by 5 to 15 mites [1, 2] with an ensuing hypersensitivity induced pruritus to the mite antigen 4 to 6 weeks after [3]. In adults, classic scabies usually spares the head/scalp and posterior aspect of the trunk. However, despite generalised pruritus and stigmata of parasitic infestation across different sites, primary lesions of classic scabies are not usually florid or diffusely confluent across all body surfaces. While secondary changes such as pruritus-induced traumatic excoriation are common in classic scabies, the primary lesions of infestation are usually localised to a small number of discrete areas. In contrast, severe scabies is defined as profuse and broadly distributed primary scabietic lesions extending to involve the face, scalp, posterior trunk and across the limbs, in addition to the sites expected in

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classic scabies [4]. Morphologically, profuse or disseminated scabies is reminiscent of classic scabies with papular, pustular, vesicular, nodular lesions usually associated with burrows.

Crusted scabies is morphologically very different to profuse scabies and while both are subtypes of severe scabies, crusted scabies is a different entity in terms of clinical presentation. 'Norwegian Scabies' was first reported by Danielssen and Boeck in 1848 [5] in patients living with Leprosy in Norway. While it is more commonly known by the preferred term 'crusted scabies' in the modern era, this is a misnomer as 'crust' specifically refers to dried proteinaceous material, usually serous, purulent, or haemoserous atop an eroded epidermis [6]. Crusted scabies specifically refers a hyperkeratotic and exfoliative dermatosis caused by the diffuse invasion of the stratum corneum of the epidermis of thousands to millions of mites [7]. This hyperkeratotic hyperinfestation of scabies is a term used to denote a severe and life-threatening form that is quite different clinically to classic or atypical variants of classic scabies including profuse scabies. It usually affects more than two sites [4] and can be localised or diffuse [8]. Both profuse and crusted scabies confer a significant risk of transmission, causing endemic community and institutional outbreaks.

17.2 Epidemiology

The worldwide prevalence of classic scabies is not described in detail [9] but international prevalence studies have suggested classic scabies was responsible for 0.21% of disability-adjusted life years from all conditions studied in the Global Burden of Disease (GBD) Study in 2015 [10]. In the late twentieth century, it was previously estimated that the global burden of disease was approximately 300 million cases of scabies, estimated to be approximately 5% of the world's population [9]. The GBD Study of 2015 confirmed that the burden of classic scabies is highest in tropical regions, especially in children, adolescents and the elderly. Overcrowded environments were also confirmed are also high risk for classic scabies [10]. The omission of crusted scabies in the GBD Study is notable and highlights ongoing challenges with accurately describing the burden of disease for this life-threatening variant [10]. The prevalence of severe scabies in both profuse and crusted forms therefore remains unknown but are both considered uncommon and rare. For example, in high-risk long term residential-care dwelling elderly patients, approximately 10% of diagnosed scabies cases were crusted, with an overall incidence of 1% of patients examined across ten institutional outbreaks in the United Kingdom [11]. In remote Northern Australia, longitudinal studies of Aboriginal patients a confirmed case rate of 1.8 to 3 per 1000 population [8, 12]. Although severe scabies is well recognised florid variant of classic scabies, without hyperkeratosis, it is a relatively recently separated subcategory that has no population data.

It is well recognised that scabies is ubiquitous worldwide and is endemic in marginalised and developing rural and urban communities [9]. Further information on the distribution and prevalence of severe and crusted scabies is required as patients with this condition are well recognised as core transmitters in their community or

living facility. People in their immediate vicinity, such as close contacts, family members and carers, suffer recurrent classic scabies, skin sores and other complications [7, 13]. Crusted scabies is highly infectious due to the extreme burden of millions of mites [7] and human to human transmission is common, if not expected [9] Classic scabies can but is not commonly associated with fomite transmission [9], but with crusted scabies mites may survive up to 7 days by feeding on sloughed skin [14] and is therefore at much higher risk of transmission to contacts via fomites. Crusted scabies was the index source of classic scabies in 83% of institutional outbreaks across 1984 to 2013 [15] and is compounded by frequent and prolonged delay in diagnosis [15, 16].

While fluctuations in classic scabies has been attributed to seasonal variations favouring cooler weather, this seasonal variation has not been investigated or reported in crusted scabies but the clustering of increased human contact in cooler weather along with increased durability and survival of the mite in cool ambient climates, may infer a similar pattern of acquisition or risk [17].

Up to half of the population of some Northern Australia's remote First Nations communities has scabies at any given time and more than 70% of children in some communities will be affected by the age of 12 months [18]. The highest prevalence of scabies reported in the general population was in Papua New Guinea (71%) followed by Panama and Fiji (both 32%) [19]. While the burden of classic scabies in developing tropical settings such as these is reported, the prevalence of crusted scabies remains unknown. These communities also have high rates of other chronic infectious, systemic inflammatory comorbidities and metabolic syndrome. It is likely that individuals with crusted scabies act as reservoirs and core transmitters for community transmission [2].

17.3 Risk Factors

Crusted scabies is usually seen immunosuppressed adults but can also rarely been seen in immunosuppressed children. It has also been reported in those with no clear identifiable risk factors or immunosuppression [20, 21]. Impairment of the host immune response causes failure of frontline control of scabies mite infestation and may be due to a variety of reasons including iatrogenic or disease-related immunosuppression, disorders of immunodeficiency, age-related immune dysregulation and chronic systemic illness. Crusted scabies is classically more commonly seen in older, frail and unwell patients. Classic associations [20] include systemic viral infections that cause reduced T-cell numbers or function, notably, human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) [22] and human T-lymphotropic virus type I (HTLV-1) [23]; other systemic mycobacterial infections including Leprosy, where this condition was first described, and pulmonary tuberculosis; autoimmune connective tissue disease including systemic lupus erythematosus and dermatomyositis [24]; conditions of frailty and vulnerability including advanced age, Down's syndrome and para/quadriplegia; and general systemic illnesses associated with multifactorial immunological deficits including

diabetes mellitus, hepatitis B, nutritional deficiencies and substance misuse [20]. The rare cases of family clustering and acquisition of severe scabies, particularly crusted scabies, in immunocompetent adults and children with suggests a more complex disease pathogenesis which may be contributed to by genetic predisposing factors that have not yet been identified [7, 20].

Although recognised as a typical risk factor for crusted scabies, this is not an AIDS-defining dermatological presentation; it does however suggest a profound immunodeficiency which may portend a poor prognosis. As with other conditions predisposed to crusted scabies, a suppressed immune status in HIV/AIDS may facilitate florid infestation by impairment of T-cell cutaneous defence. This includes reduced/absent itch as the consequence of impairment of the expected hypersensitivity to the mite antigen, which would otherwise help to alert the patient to the presence of the mite and scratch and attempt to control the mites through traumatic excoriation. Dysregulated potentiation of TH2 cytokine profile which may facilitate hyperkeratosis. Furthermore, florid severe scabies occurs in HIV/AIDS and other systemic viral disorders of T cells including HTLV-1 [25].

Local and widespread abnormalities of the peripheral nervous system with sensory and/or motor deficits predispose individuals to crusted scabies. This may include para/quadriplegia, peripheral neuropathy secondary to causes including malnutrition, degenerative neuropathies, infectious neuropathies and defects of cutaneous sensation/integrity such as burns and primary dermatoses. The lack of both sensory input to perceive itch and motor deficits to scratch contributes to failure of local mechanisms to control scabies that healthy people are afforded [26].

Crusted scabies, first reported in people living with leprosy may present in patients that have both active as well as treated and resolved leprosy with and without a sensory neuropathy, suggesting that the immune defect that may have predisposed to leprosy in the first place may be at play in crusted scabies [2, 27] Classic scabies and its severe exuberant variant remain common in patients living with leprosy and its complications [28] but crusted scabies is seen with relatively high frequency.

Transplant patients require immunosuppressive medications that protect against T-cell-mediated acute allograft rejection and include calcineurin inhibitors, azathioprine, mycophenolate mofetil which disrupt T-cell activity [29]. This predisposes transplant patients, both solid organ and haematopoietic, to crusted scabies as T-cell dysfunction is responsible, at least in part, for this condition.

Risk factors in children parallel the adult population and include haematological malignancies such as acute lymphoblastic leukaemia [30], solid organ and bone marrow transplant [31], HIV and AIDS [32, 33], systemic inflammatory conditions requiring immunosuppression including juvenile idiopathic arthritis [34] and Down's syndrome [35]. The high prevalence of atopic dermatitis in childhood associated with overenthusiastic use of topical corticosteroid and topical immunomodulatory preparations has also been associated in children presenting with severe and crusted scabies [36].

Aboriginal Australians in northern tropical Australia suffer with some of the highest documented rates of crusted scabies and is a contributing factor to high rates

of community transmission of classic scabies. While predisposing immunosuppressive risk factors are identifiable in this population including disease-related and iatrogenic immune dysregulation; chronic systemic liver and renal disease; comorbid infectious diseases including leprosy; and substance misuse, clear risk factors have not been identifiable in 42% of patients in this group.

Cases of crusted scabies in patients with no identifiable immunosuppressive predisposition and family clustering highlight the importance of ongoing investigation into the genetic factors such as hereditary immune defects that may contribute to acquisition of this disabling and life-threatening condition [2, 7].

Like crusted scabies, immunosuppression is a common risk factor for atypical and florid presentations of scabies. As such, marginalised populations appear to be more readily affected which may include predisposing patient factors such as comorbid systemic disease and iatrogenic immunosuppression, location-related factors such as tropical climates, and environmental factors such as overcrowding associated with disadvantage. For example, systemic lupus erythematosus is two to four times more common in Australian and New Zealand Indigenous populations [37, 38] where scabies is known to have a significantly higher incidence.

RISK FACTORS FOR CRUSTED SCABIES

DISEASES-RELATED IMMUNE DYSREGULATION

- T-cell dysregulation
  - HIV/AIDS [22, 25, 39]
  - HTLV-1 [40, 41]
  - Cutaneous T-cell lymphoma [42]
- B-cell dysregulation
  - Systemic lupus erythematosus [21]
  - Dermatomyositis [24]
  - Acquired selective IgA deficiency
  - Cutaneous vasculitis
  - Autoimmune polyglandular syndrome [43]
- General disease-related immunologic compromise
  - Haematological malignancies (e.g. ALL, adult T-cell leukaemia/lymphoma) [41, 44–46]
  - Langerhans cell histiocytosis [47]
  - Graft-versus-host disease
  - Diabetes mellitus
  - Hepatitis C [48]
  - Inherited disorders of immune deficiency

IATROGENIC IMMUNOSUPPRESSION

- Transplant (e.g. renal, bone marrow) [29]
- Cytotoxic chemotherapy agents and chemoradiation therapy [49]
- Systemic immunosuppression/immunomodulatory treatments including systemic corticosteroids and monoclonal antibody therapies [50–53]
- Topical corticosteroids and other topical immunomodulatory treatments [36, 54]

NUTRITIONAL DEFICIENCIES

Beriberi, kwashiorkor [55] (Strobel), vitamin A deficiency [56, 57], mixed malnutrition [58]

DEFECTIVE CUTANEOUS SENSATION OR DEFECTIVE CUTANEOUS INTEGRITY

Leprosy [59]
Syringomyelia [60]
Tabes dorsalis
Para/quadriplegia [61, 62]
Burns [63]
Epidermolysis bullosa [64, 65]

STATES OF MENTAL/COGNITIVE DISABILITY OR INCAPACITATION

Elderly [66]
Bedbound [67]
Parkinson's disease [68]
Down's syndrome [67, 69]
Mental disabilities including cognitive, learning, and mental health disorders [67]
Substance abuse [70]

OTHER ENVIRONMENTAL RISK

Overcrowding [71, 72]
Poor sanitation [9, 71]
Institutionalisation [71]
Hot/humid ambient climate [20]
Indigenous communities [20]

RARE

Immunocompetent adults [73] and children [21]
Familial [2]
Pregnancy [74]
Neonates [75]

17.4 Pathophysiology

Severe and crusted scabies are caused by the same ectoparasite that causes classic scabies. The difference in clinical appearance is attributable to differences in host immune response. In terms of the mite itself, scabies mites usually live up to a maximum 3 days, usually 24 to 36 h [26] off a human host, but those from patients with crusted scabies may live up to 7 days by feeding on sloughed skin [14]. It is an obligate parasite. The hypersensitivity response to classic scabies' 5 to 15 mites [9] facilitates itch which assists in traumatic/mechanical excoriation to attempt to control the mite. Mite proliferation is controlled by an intact host immunity. Crusted and severe scabies occurs in patients with immunodeficiency, neurological disease causing reduced sensation, immobility with reduced ability to scratch, or in genetically susceptible patients [26].

It is uncommon for crusted scabies to result as a progression from classic scabies [7], whereas severe scabies may develop in a similar fashion, albeit more florid in its presentation, and may be an initial presentation or a severe deterioration from a classic case. In the context of disruption to the normal functioning of the immune system, the development of a hypersensitivity response is impaired [76]. As a result, pruritus is often minimal and as such, the absence of scratching and inflammation is a favourable environment for the proliferation of mites [30].The result is crusted scabies is caused by hyperinfestation of millions of mites [7] which has been previously quantified to be approximately 4700 mites g^{-1} of skin [77]. Animal studies have shown that symptoms start 4 weeks post-infestation, and crusted plaques appear usually 8 to 12 weeks later [78].

From a cellular pathogenesis perspective, in studies of lesional skin biopsies, classic scabies infestation usually manifests with a dominant dermal infiltrate of $CD4^+$ T lymphocytes at a reported CD4/CD8 ratio of 4: 1 [78, 79] which overlaps with the profile of atopic dermatitis [79, 80], explaining the phenotypic overlap of pruritic papular excoriations. However, psoriasis and crusted scabies, diseases which both manifest with significant hyperkeratosis, demonstrate a dermal infiltration of $CD8^+$ T lymphocytes and an absence of B cells [7] with normal peripheral blood results for these lymphocyte subsets. Prominent keratinocyte derived proinflammatory cytokines involved in studies of CS showed a heightened expression of IL-1β and TGF-β which may be responsible for T-cell activation and skin homing of $CD8^+$ T lymphocytes [7]. This supports the hypothesis that classic scabies is associated with a T-helper (Th) type 1 (Th1) response (cellular) and crusted scabies is associated with a Th2 response (humoral) [7] and disease presentation is dependent on the pathway in which the mite antigens are processed. While the role of these skin homing cytotoxic $CD8^+$ T lymphocytes is yet to be fully elucidated in crusted scabies, mechanisms of tissue damage may include direct cytotoxicity against keratinocytes and release of cytokines, which could amplify the inflammatory response by targeting resident skin cells [7]. IL-1β, produced by epithelial cells and macrophages and commonly seen in systemic disorders of inflammation, is responsible for T-cell activation and is seen in lesional skin of crusted scabies. TGF-β is recognised as an immunosuppressive cytokine which specifically *suppresses* the function of proinflammatory function of Th1 lymphocytes which impairs local immune control as well as augments the shift towards a Th2 pathway. Furthermore, TGF-β helps differentiation of naïve T cells to Th17 T cells that secrete IL-17A, IL-17F, IL-21 and IL-22. Th17 cytokines can be important in host defence against some infections, but in the inappropriate context, development of Th17 cells could lead to increased disease progression, chronic infection rather than remission and clearance, and has no protective benefit [78]. Additionally, IL-17 is a key cytokine that contributes to keratinocyte proliferation and epidermal hyperplasia observed in psoriasis and inherited ichthyoses [81], which despite its differing aetiology, has clinical overlap with crusted scabies [78]. IL-17 may be secreted/expressed from the $CD8^+$ T lymphocytes, but may also be released by other cells including mast cells which are increased in crusted scabies [78].

Furthermore, the Th2 cytokine milieu, including peripheral blood mononuclear cell populations that liberate IL-4, IL-5, IL-13, may explain an elevation in *S. scabiei* antigen-specific IgE production [82, 83]. IgG4 is often concomitantly produced but the role of this cytokine in crusted scabies remains yet to be clarified. Upregulated Th2 cytokines seen in crusted scabies including IL-4 may also drive keratinocyte hyperproliferation as is the case with localised IL-17-secreting T cells [78]. Paradoxically, despite elevated peripheral IgE and IgG4 levels in patients and animal models with crusted scabies, B lymphocytes and plasma cells are absent in lesional skin samples which may represent the failure of local and specific targeted skin immune responses and therefore may explain the failure of skin immunity to mount an effective cutaneous response to control scabietic infestation and allowing uncontrolled proliferation.

Shifts to Th2 and increased secretion of IL-17 may both contribute to the pathogenesis of crusted scabies and may represent novel treatment targets, which have been of significant benefit in psoriasis and some ichthyoses [81].

Regarding secondary infection as a complication of established severe and crusted scabies, first-line innate immunity defences promote protective inflammatory responses in an attempt to control the infestation of invading parasites. The innate immune system includes the complement pathway protects and combats against ectoparasitic invasion and bacterial infections [13].

Innate complement defences are impaired from being activated as well and impairs the interaction with host regulators of complement [13]. Scabies mites express regulatory and inhibitory surface proteins that inhibit activation of the complement cascade at different key rate limiting steps particularly the formation of the final step of the membrane attack complex to evade elimination and allow survival [84]. These external pathogens' complement evasion strategies not only potentiate scabies infection and mite proliferation but also synergise to create a favourable environment for secondary bacterial co-infection in the context of scabies infestation [13] may lead to both superficial pyoderma and systemic bacteraemia with sepsis, which is associated with all forms of scabies. Secondary bacterial pathogen invasion and subsequent superficial or systemic infections, scabies mites have been shown to secrete specific complement inhibitors into established burrows, which potentially facilitates the establishment of secondary streptococcal and staphylococcal infections which are responsible for subsequent invasive bacterial disease which Furthermore, the tendency for areas of profound hyperkeratosis to create fissures provides direct entry portals for secondary bacterial infection [2]. Impaired healing of fissures and ongoing risk of infection is expected with many of the predisposing comorbidities including peripheral neuropathy and malnutrition associated with chronic systemic disease.

These factors contribute to the mortality associated with crusted scabies [13, 84]. When immunity is impaired, as is usually the case in crusted scabies, combined with grossly dysregulated epidermal integrity, this is the ideal milieu for the propagation of both infections [13, 84]. Co-infection of both scabies and bacteria may therefore be mutually beneficial for the propagation of both in the same host.

17.5 Clinical Features

There is a continuum between classic and severe classic scabies, with the latter being a florid and generalised variant, as opposed to localised to limited typical areas such as interdigital spaces, acral surfaces, periumbilical area and genitals. Crusted scabies presents differently in its morphology and distribution as well as complication rates and types. Particularly atypical presentations of crusted and severe scabies may manifest in immunocompromised children and adults and may present in ways that mimic multiple infectious and inflammatory dermatoses.

17.5.1 Severe Scabies

Severe scabies affects areas more broadly distributed than the typical sites which normally affect classic scabies. Severe forms involve all body surfaces including typically spared sites such as the posterior trunk/back, the head and neck area and nail unit [26]. Depending on patient factors it may or may not be severely pruritic. It is much more difficult to eradicate than classic scabies.

17.5.2 Crusted Scabies

The symptoms and signs of crusted scabies can vary in each individual patient which contributes to the difficulty and delay in diagnosis. While it is often reported that crusted scabies is not always characterised by the extreme and disruptive pruritus of classic scabies, pruritus is variable in its intensity and can be experienced by more than 50% of affected patients [20].Itch can be intermittent or mild but does tend to follow the nocturnal exacerbation pattern demonstrated in classic scabies. Patients may also or instead complain of the thickening and callous like changes [85] that may be unsightly or functionally disruptive. Patients complaining of symptoms tend to seek review on average weeks to months after the onset of the rash [29]; however, due to the rarity of the condition, lack of awareness of the condition, and broad differential, delayed diagnosis in the norm [29, 43, 86] and can be as long as several months to many years (one patient reported to have suffered with crusted scabies for 11 years [43]. Patients that are asymptomatic or only experiencing mild pruritus may have a more prolonged course to diagnosis. Crusted scabies is often erroneously treated with non-targeted topical agents, systemic corticosteroids, retinoids, immunosuppressants and phototherapy.

While classic scabies tends to not affect areas with dense pilosebaceous units [87], crusted scabies can floridly affect and localise to the head and neck area, most notably the scalp [4, 88–91] and may include hair shedding (Fig. 17.1) [2, 85], face [4, 89, 92] including as widespread as the eyelids (Fig. 17.2) [2]; the trunk including the periumbilical area (Fig. 17.3); bony prominences (finger articulations, elbows, iliac crests [26]; both extensor and flexural limbs [26, 67] (Fig. 17.4); fingers/toes/palms/soles (Figs. 17.5 and 17.6) [4, 29, 89, 91, 93–95], nail units [7, 45, 96] and

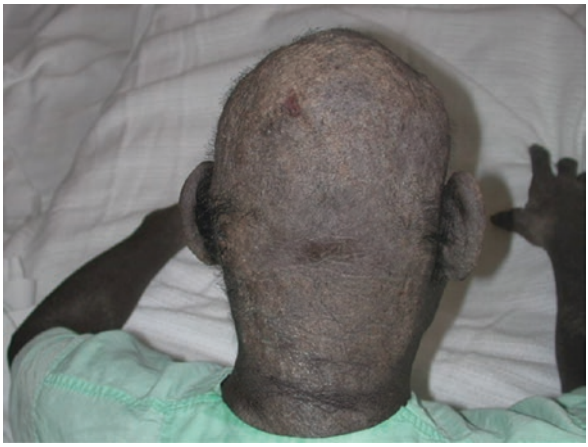

Fig. 17.1 Diffuse poorly defined hyperkeratosis of the scalp and ear helices

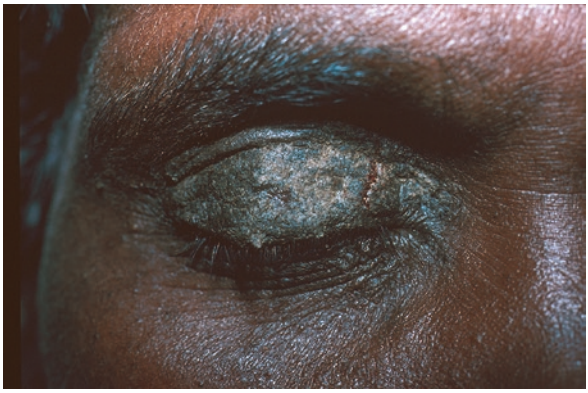

Fig. 17.2 Crusted scabies of the upper eyelid with poorly defined hyperkeratotic plaque

genitalia [89, 97–99]. Crusted scabies may however be poorly demarcated, generalised and widespread, affecting all body surfaces [26, 39, 96] and associated with erythroderma [35, 73, 100, 101].

The primary morphology of 'crusted' scabies is grey to cream to yellow to brown psoriasiform hyperkeratotic plaques usually with background changes of erythema [26, 102]. The erythematous changes may be difficult to appreciate in skin of colour. The hyperkeratotic scale may be loose, scaly, flaky and easily removed/self-exfoliative that may lifting without bleeding (Auspitz negative) or thick and adherent [7]. Large malodorous plates of scale with fissuring [68] are common and represent severe disease with a portal of entry for secondary bacteraemia [2, 7, 11, 26, 41].

Initial stages of infestation may be misleading as very discrete areas of focal hyperkeratotic change with or without more classic manifestations of classic scabies. Localised areas may be small erythematous papules [86], focal areas of verrucous hyperkeratosis, larger more exuberant nodular hyperkeratotic mounds or

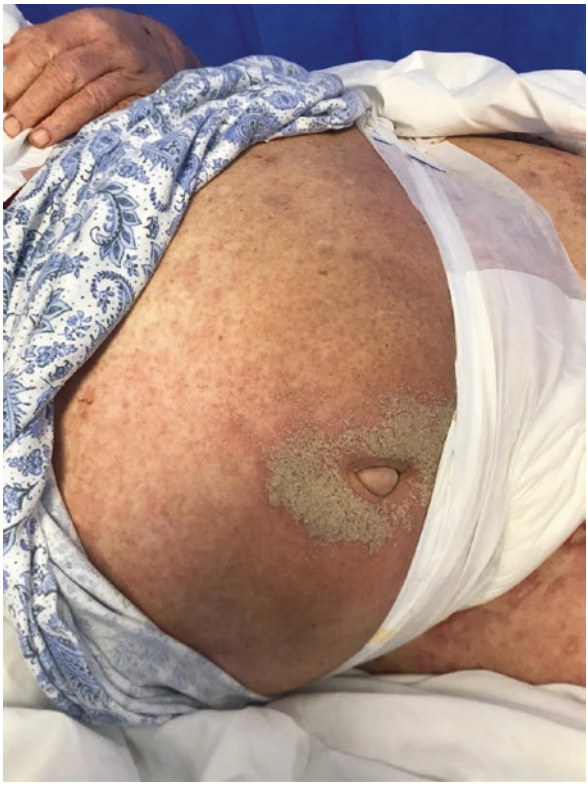

Fig. 17.3 Periumbilical crusted scabies

guttate lesions [29]. Exuberant exophytic hyperkeratosis can be easily confused with viral verruca or hereditary disorders with verrucous like changes [103]. These focal and localised changes are usually progressive in a subacute and insidious with a chronic course as compared to classic scabies which is acute [29, 43]. Crusted scabies may however, on occasion, present in a florid, eruptive and widespread manner, demonstrating rapidly evolving widespread plaques that may be broad and diffuse hyperkeratotic sheets. The classic appearance is of a psoriasiform dermatitis [104] but may be eczematous, contact-dermatitis-like [105], erythrodermic dermatitis [35, 106], morbilliform, pityriasis rosea-like [107], Darier disease-like [108] or bullous pemphigoid-like [109].

Crusted scabies usually does not demonstrate classic burrows as these small curvilinear structures are obscured by the hyperkeratosis. However, burrows with classic dermoscopic evidence of the 'delta sign' may be seen in overlap states with crusted scabies and severe variants of classic scabies [43].

Manifestations of systemic illnesses and complications associated with crusted scabies are often noted and include lymphadenopathy, oral mucosal changes including atrophic glossitis and angular cheilitis [43], generalised oedema/anasarca, cachexia and general malaise/fatigue.

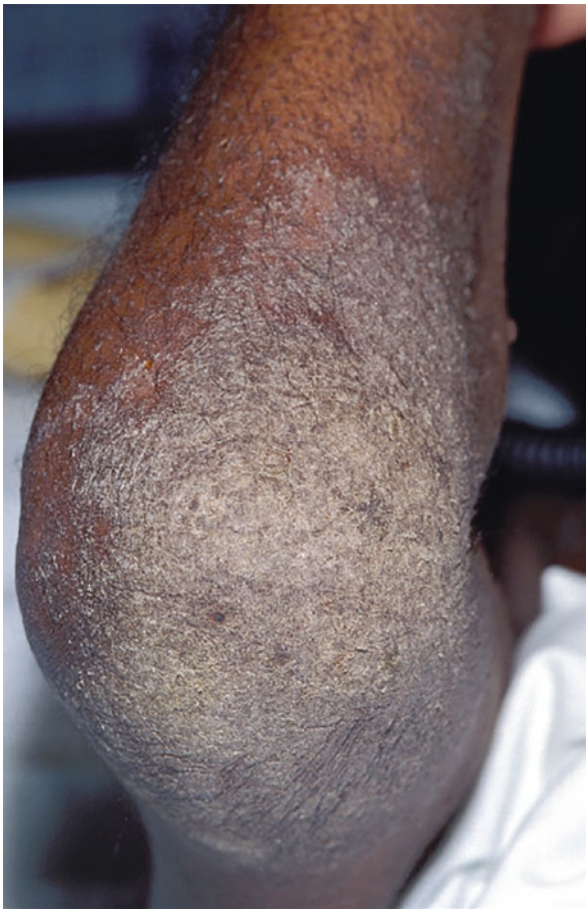

Fig. 17.4 Psoriasiform hyperkeratotic plaque on extensor elbow in crusted scabies

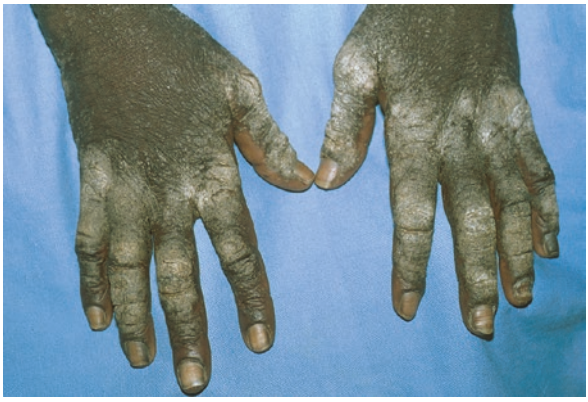

Fig. 17.5 Sharply demarcated moderately severe crusted scabies of the dorsal fingers

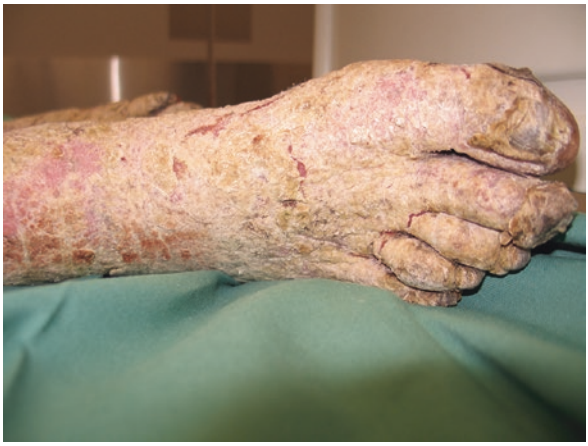

Fig. 17.6 Grade three severe crusted scabies with obliteration of the nail unit

17.5.3 Special Sites and Their Features That May Assist Clinical Diagnosis

17.5.3.1 Head

The face and scalp are common sites of localised infestation, in contradiction to classic scabies, where these sites are usually spared [88, 89, 110].Severe scabies may manifest on the face and scalp alone, particularly in immunosuppressed patients and infants, or may be part of more widespread distribution with involvement of the head and neck [51]. Patients with exclusive scalp involvement in isolation have been reported as showing seborrhoeic dermatitis-like scalp changes with both crusted and severe scabies and has generally been reported in immunocompromised marginalised population patients [111] and in paediatric patients undergoing chemotherapy for haematological malignancies [30] without evidence of the hyperkeratotic psoriasiform plaques of crusted scabies or severe scabies in other locations. Scalp changes may mimic the non-specific scalp dermatitis of dermatomyositis [24] in crusted scabies and may represent overlap in patients with both crusted scabies and concomitant dermatomyositis with disease-related and iatrogenic immune dysregulation. Diffuse facial involvement including eyelids, eyebrows and ears [2, 45, 85, 86] is a hallmark of particularly severe and advanced disease. Beyond mild involvement, moderate to severe scalp and facial involvement is usually associated with non-scarring alopecia of the scalp and brows [85, 90].

17.5.3.2 Hands, Feet and Nails

Involvement of hands and feet, including the nail units, are common sites of localised involvement of both severe and crusted scabies but may also be involved in widespread disease. In terms of glabrous acral skin surfaces, the hyperkeratosis may manifest as a palmoplantar keratoderma, distributed in a ‘reverse’ pattern to classic focal keratodermas with accentuation over the areas of *least* friction such as the non-weight-bearing plantar arch and under the proximal phalanges (Figs. 17.7 and 17.8) [94].

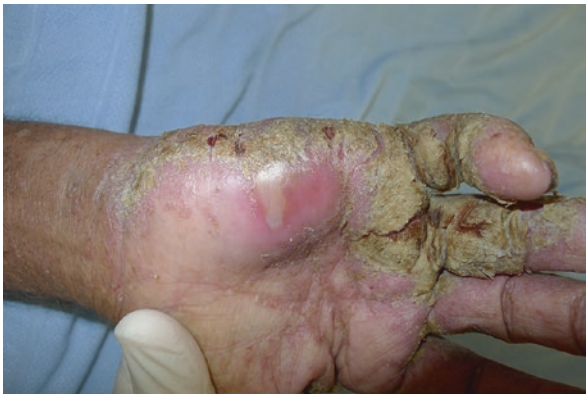

Fig. 17.7 Fissured and secondarily infected crusted scabies localised to the hand sparing pressure sites on palms

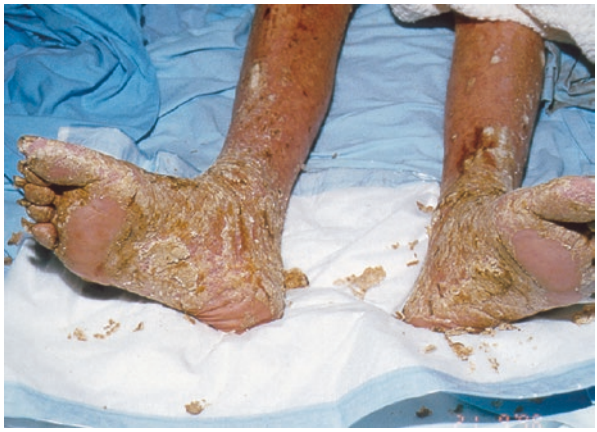

Fig. 17.8 Severe reverse plantar keratoderma with sparing under the sites of pressure and significant parasitic onychogryphosis fatality secondary to sepsis

Acral distribution is often associated with periungual erythema and swelling [45] and grossly thickened nails. Involved nails are often dystrophic with abundant, persistent and treatment refractory hyperkeratotic subungual debris [22, 45, 85, 96, 110]. Nail dystrophy in isolation without evidence of more extensive scabies (classic or severe/crusted) of the skin and can include onycholysis, with and without periungual infection, subungual hyperkeratotic debris, nail plate deformity/hypertrophy, longitudinal nail splitting, yellow–green–brown nail discoloration and periungual scale and crusting (Figs. 17.9, 17.10, and 17.11) [112]. Relapses are common with nail disease and require oral and topical treatment to prevent treatment failure [113].

17.5.4 Clinical Presentation for Special Populations

17.5.4.1 Paediatric Patients

Widespread and severe scabies may be seen in children due to the premature pilosebaceous units and low activity of these structures in paediatric skin. Furthermore, neonates and infants have immature immune systems and are unable to defensively

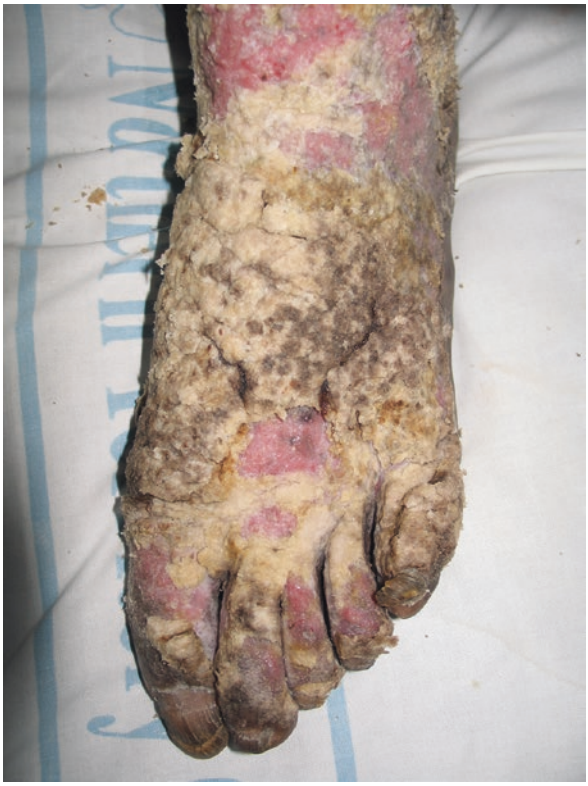

Fig. 17.9 Severe grade three hyperkeratosis, depigmentation and subungual hyperkeratotic debris

scratch. When combined with high mite exposure and other comorbidities, may be prone to development of severe or crusted scabies, also complicated often by delayed diagnosis and obfuscation of the issue by trials of various topical treatments [68, 114]. This is an exceptionally rare diagnosis in children, particularly otherwise healthy children (Fig. 17.12).

Severe scabies in children, referred to as 'whole body' scabies, associated with life-threatening systemic complications and repeated hospital admissions has been noted in Australian Aboriginal communities where scabies, included crusted and classic, is endemic [8]. Manifestations of severe scabies in children include widespread erythrosquamous flexural and truncal/facial eruptions, mimicking eczema, hyperkeratotic lichenified areas on acral surfaces and/or diffuse excoriated papulonodular lesions associated with vesiculation and crusting (Fig. 17.13) [36].

Analogous to adult presentations, children tend to be immunosuppressed for hereditary, acquired and iatrogenic reasons and present with hyperkeratotic psoriasiform dermatitis on localised or generalised skin surfaces. Divergent presentations may include verrucous plaques on the dorsal joint spaces on the hands and medial feet, which is easily confused for common warts seen in children which are also common with immune dysregulation for any reason. Other common presentations which have mimics seen commonly in children include seborrheic dermatitis like

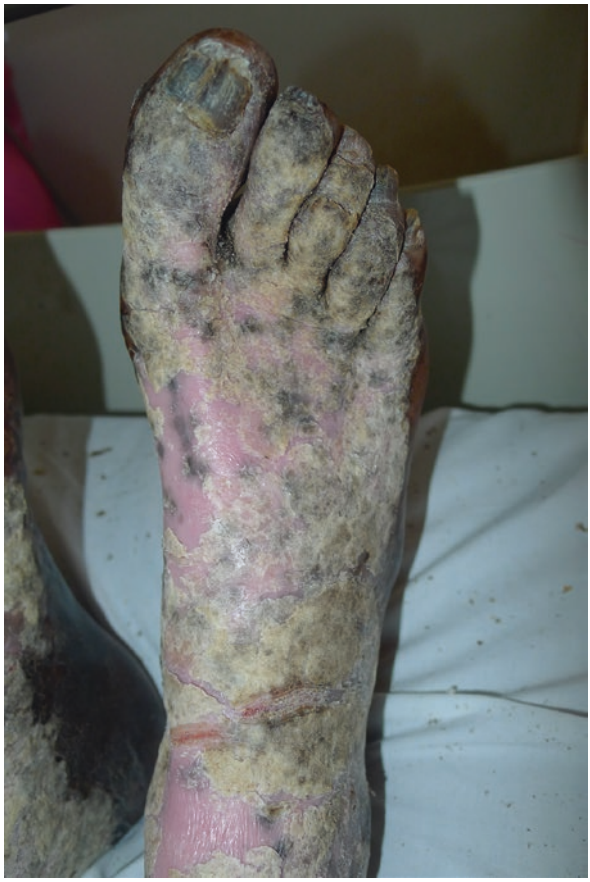

Fig. 17.10 Mottled dyschromia, fissuring and hyperkeratotic plaques in crusted scabies

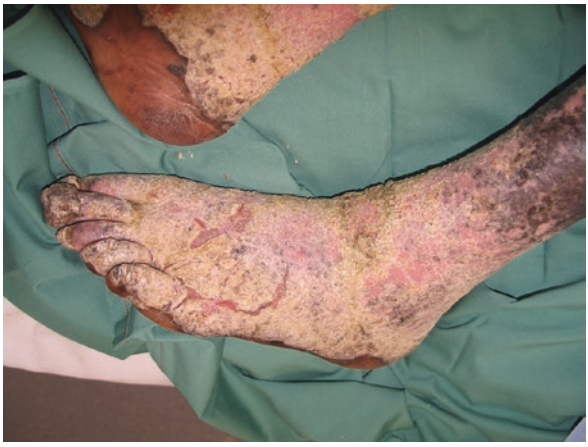

Fig. 17.11 Severe hyperkeratosis with exfoliation, fissuring, depigmentation and nail dystrophy

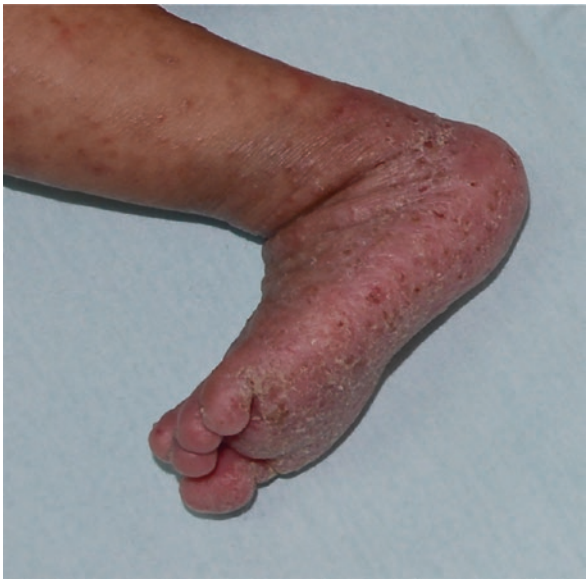

Fig. 17.12 Severe and crusted scabies in an immunocompetent infant

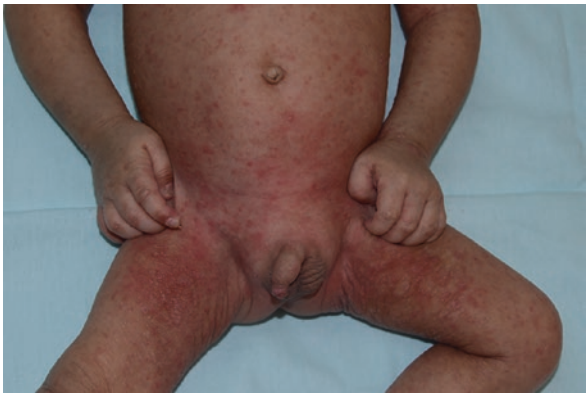

Fig. 17.13 Severe scabies in an immunocompetent infant

scalp changes [30] and fine exfoliative scalp scale. Erythrodermic severe and crusted scabies [101] is often diagnosed as being secondary to common causes of rashes in children and include psoriasis [35] and eczema. Similar to adults, nail involvement may present with dystrophy and thick hyperkeratotic subungual debris, but also may have thick verrucous subungual plaques and yellow discoloration [113].

17.5.4.2 HIV/AIDS

Both generalised severe and crusted scabies can present in an atypical [25] and/or widespread manner [39] in patients living with HIV/AIDS, and thus, a low threshold for suspicion of a parasitic infestation is required in patients with this spectrum of comorbid immunodeficiency. The clinical presentation may vary to include generalised pruritus with scant but widespread papular lesions, some of which may

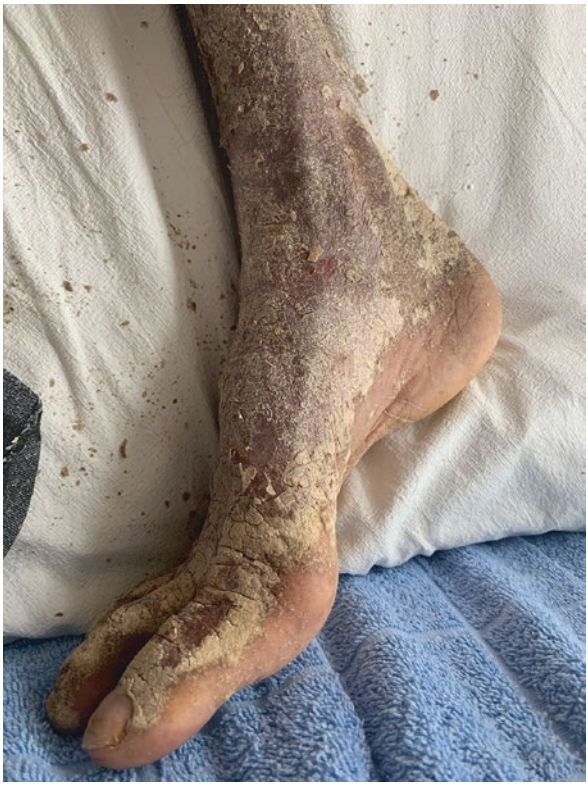

Fig. 17.14 Crusted scabies in patient with AIDS showing significant exfoliation and fomite infestation

mimic florid Darier disease, along with the more typical hyperkeratotic psoriasiform plaques of crusted scabies [22] (Fig. 17.14). These changes can be easily attributed to seborrhoeic dermatitis, florid psoriasis and the generalised pruritus of AIDS all of which are common dermatological manifestations of this spectrum of disease and may contribute to delayed diagnosis and treatment [22]. Occult presentation in atypical sites requires full skin examination in high-risk patients from scalp to toes including the genitals, where appropriate. Diagnosis of classic scabies in contacts may heighten the clinician's attention to possible index case of mis/undiagnosed severe or occult crusted scabies people living with HIV/AIDS who have unusual and undifferentiated skin eruptions [43]. Therefore, a full family and social history is important to minimise the chance of missed or delayed diagnosis.

17.5.4.3 Elderly and Immobile Patients

Post cerebrovascular accident or brain/spinal cord trauma, scabietic lesions including crusted scabies have been reported to preferentially manifest on the affected areas [2, 62, 115].

Elderly [66], immobile and profoundly physically or cognitively disabled patients alike have multifactorial comorbidities. Depressed immunity, including

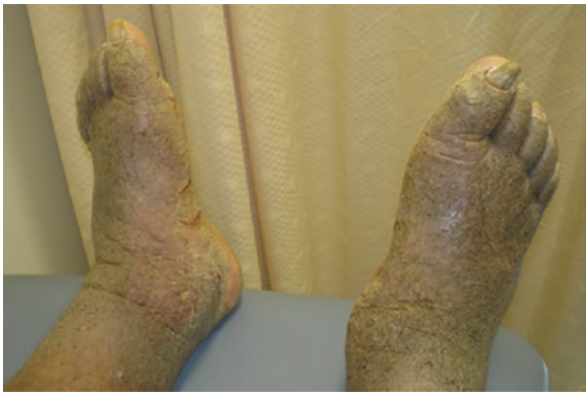

Fig. 17.15 Diffuse hyperkeratosis and fissuring in crusted scabies

iatrogenic, age-related, or disease-related immunosuppression; motor and/or sensory neuropathies leading to impaired sensation of itch and inability to scratch; and comorbid nutritional deficiencies are contributors (Fig. 17.15).

17.5.4.4 Pregnancy

Crusted scabies in pregnant women is exceedingly rare and only one case report is seen. Evaluation for occult contributors would be prudent [3, 74].

Clinical differential diagnoses of severe scabies	**Clinical differential diagnoses of crusted scabies**
Arthropod bite reaction including to midges, fleas, bedbugs, mites, lice	Psoriasis
Folliculitis	Eczema (atopic, allergic, irritant)
Eczema (atopic, allergic, irritant)	Seborrhoeic dermatitis
Prurigo nodularis	Drug eruptions (particularly exfoliative erythrodermic variants)
Lichen planus	Pityriasis Rubra pilaris
Drug eruption	Cutaneous lymphomas (e.g. erythrodermic mycosis fungoides or Sezary syndrome)
Viral exanthema	Dermatophyte infection
Primary or disseminated varicella zoster	Darier's disease
Tungiasis	Dermatomyositis
Dermatophyte infection	Systemic lupus erythematosus
Bullous pemphigoid	Inherited and acquired palmoplantar keratodermas (e.g. Unna-Thost palmoplantar keratoderma; acrokeratosis paraneoplastica)
Dermatitis herpetiformis	Inherited and acquired conditions of nail dystrophy (e.g. pachyonychia congenita, traumatic nail dystrophy)
Pemphigus vulgaris or foliaceus	Senile pruritus
Grover's disease	
Acute reactive perforating collagenosis	
Lymphomatoid papulosis	
Langerhans cell histiocytosis	
Eosinophilic folliculitis	
Pityriasis rosea	
Delusional infestation with neurotic excoriation	

17.5.4.5 Proposed Grading of Severity and Implications for Treatment: See Chap. 25 for More Detail

A proposed severity grading method guides the duration and intensity of treatment and should establish disease status at presentation [116]. Severity grading does not necessarily predict the likelihood of life-threatening complications [116] but is a useful tool to stratify patients into mild (grade one), moderate (grade two) and severe (grade three). It is calculated on four criteria: distribution, scale/shedding, previous episodes/recurrence and skin integrity.

17.5.4.6 Complications

Underlying comorbidities in patients suffering with severe and crusted scabies has a significant impact on the likelihood of both simple or complex and life-threatening complications. Similar to data on epidemiology, mortality related to classic scabies more broadly is not well quantified [117], but even less so for severe and crusted scabies. The specific mortality for crusted scabies is poorly understood in some studies has been shown to be up to 50% and is attributable to secondary complications from breakdown in cutaneous integrity and bacteraemia [3, 20, 77, 117]. In one study, grading of the severity of the presentation did to not correlate with or impact death rates or readmission rates [116], but features such as erythroderma, fissured and infected crusted scabies have a higher chance of the development of bacteraemia, thermodysregulation and treatment failure.

17.5.5 Secondary Infectious Complications

17.5.5.1 Bacterial

In classic scabies, particularly tropical areas and developing communities with suboptimal social infrastructure and housing, secondary pyoderma is common and caused by *Staphylococcus aureus* and *Streptococcus pyogenes* [118, 119].In crusted scabies, *Staphylococcus aureus* bacteraemia is the main cause of infection-related mortality [117], but bacterial sepsis can also be caused by other skin organisms such as staphylococcus epidermidis [58] and pseudomonas aeruginosa [120]. Bacterial infectious complications has broad clinical presentations and can include simple impetigo, abscesses/boils, ecthyma, cellulitis, lymphangitis [121] and fatal infectious complications including cerebral abscesses [122] in addition to multiorgan dysfunction from bacteraemia.

An Australian study over a 10-year period showed that 11% of cases of crusted and severe scabies over were shown to develop secondary *Staphylococcus aureus* bacteraemia, with 7% of this group dying from sepsis within 30 days. This had a higher one-year mortality of up to 26% which was higher than that for matched patients undergoing haemodialysis or limb amputations [117]. This is likely due to a combination of secondary bacterial sepsis, deterioration of predisposing comorbidities, fluid and electrolyte abnormalities, treatment delay and general deconditioning from severe illness [20, 117, 119].

17.5.5.2 Viral

Scabies herpeticum is an extremely rare presentation of Kaposi's varicelliform eruption whereby the crusted scabies is secondarily infected with herpes simplex viral infection. It was first described in 1992 [123] and presents in profoundly immunosuppressed patients such as those with HIV/AIDS, haematological malignancies and transplants [124, 125]. The herpetic lesions may be localised or disseminated with multiorgan dysfunction. Presentation is that of classically vesiculated herpetic lesions and punched out clean-based ulcers, which may coalesce to ulcerated plaques with concomitant hyperkeratotic plaques of crusted scabies peripherally. This is a very poor prognostic sign.

17.5.5.3 General Risks

High output cardiac failure, electrolyte disturbances, generalised oedema/anasarca, sleep deprivation and cachexia are all complications of significant compromise in cutaneous integrity and contribute to mortality alongside bacteraemia. Delayed diagnosis and delayed implementation of appropriate treatment of the individual, the environment and the contacts lead to further progression and dissemination of the infestation, increased risk of sepsis, increased risk of death and ongoing community/institutional transmission and outbreaks [96]. Under treatment, particularly of difficult sites such as subungual areas, failure to treat contacts also leads to risk of treatment failure.

17.5.5.4 Skin Specific

Chronic dermatoses, particularly in skin of colour, may be complicated by chronic hyper and hypopigmented changes (Figs. 17.16 and 17.17). Post-scabietic pruritus is not uncommon in patients manifesting initially as a pruriginous dermatosis [109].

17.5.5.5 Stigma

Severe scabies is associated with significant stigma and psychological distress due to shame and ostracism. These impacts must be considered as part of holistic patient care [8, 71, 126, 127].

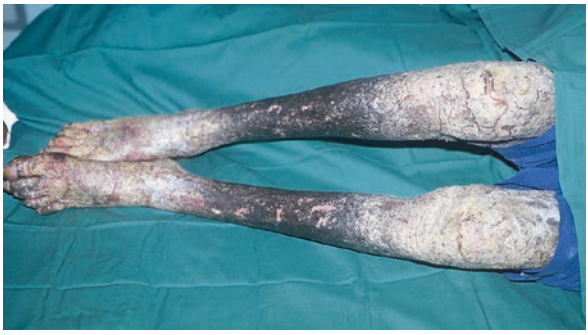

Fig. 17.16 Extensive grade three crusted scabies with deep fissuring on extensor knees and dorsal feet and patchy depigmentation

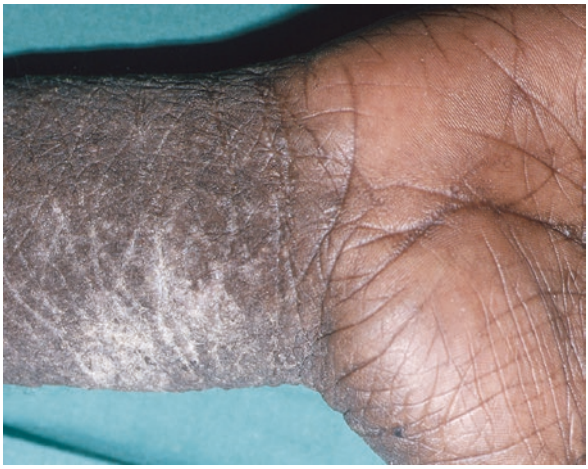

Fig. 17.17 Subtle psoriasiform hyperkeratosis of localised crusted scabies associated with subtle hyperpigmentation and hypopigmentation

17.6 Diagnosis

Improved awareness and clinical suspicion of atypical scabies is imperative to its diagnosis.

Missed diagnoses contribute to morbidity, community transmission and economic burden [128].

Frontline and general medical staff need education and access to early involvement of dermatological and infectious disease teams in order to facilitate appropriate investigations and confirmation of severe and crusted scabies.

Regardless of atypical symptom profiles or protean clinical examination findings, it is important to ensure scabies and its clinical variants are excluded in patients presenting with itch or new unexplained cutaneous eruptions. While typical crusted scabies may be easily diagnosed by the trained eye, the atypical presentations may masquerade delaying diagnosis (Figs. 17.18 and 17.19, same patient).

Simple bedside tests and formal investigations are helpful in confirming the diagnosis, especially when undertaken by trained health care workers. There is no standardised clinical diagnostic algorithm for severe or crusted scabies [128], and international consensus criterion for the diagnosis of scabies is not intended for use in atypical, severe or crusted variants [16]; however, microscopic visualisation of parasites or their products is considered the gold-standard investigation for diagnostic confirmation of all forms of scabies [129].

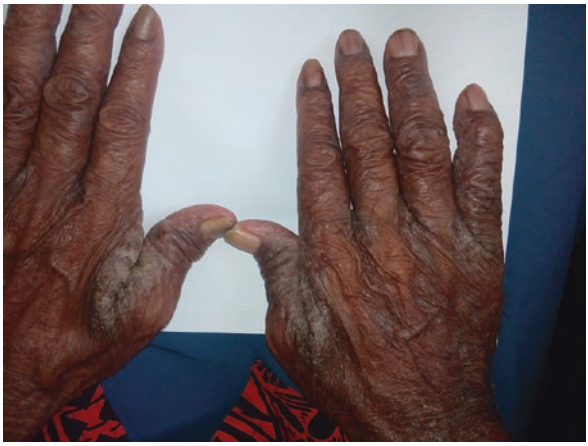

Fig. 17.18 Subtle presentation of grade one crusted scabies dorsal hand

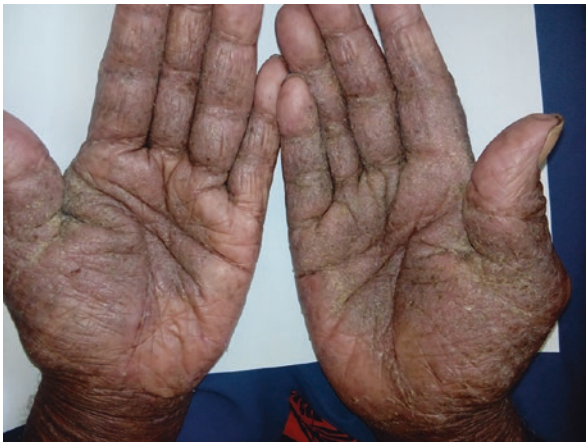

Fig. 17.19 Subtle psoriasiform hyperkeratosis of grade one crusted scabies on the palmar hand

17.7 Confirmatory Diagnostic Methods

Skin scrapings visualised with microscopy to confirm the presence of mites, eggs and faeces is gold-standard confirmatory evidence of scabietic infestation across all clinical types [129, 130] (Figs. 17.20, 17.21, and 17.22). Preferable locations include the acral surfaces and genitals [109] where looking to identify more classic burrows, but all hyperkeratotic areas of crusted scabies should be high yield. It is commonly performed with potassium hydroxide 20%; however, this can dissolve faecal pellets and therefore mineral oil is the best vehicle to suspend skin scrapings within [129, 130]. Furthermore, mineral oil is highly refractile and allows visualisation of the mite and its products better. Mineral oil may be applied directly to suspect areas and then scraped with a blade to remove the mite from the papule at the end of the burrow. To enhance diagnostic accuracy, the distal end of the burrow can be opened with a fine needle to bring the mite to the surface [26]. Alternatively,

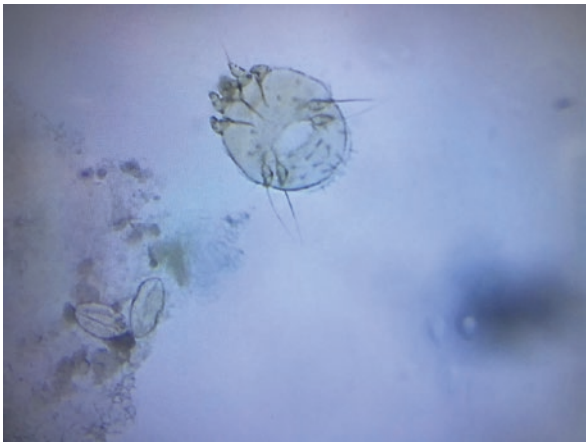

Fig. 17.20 Scabies, eggs, faeces

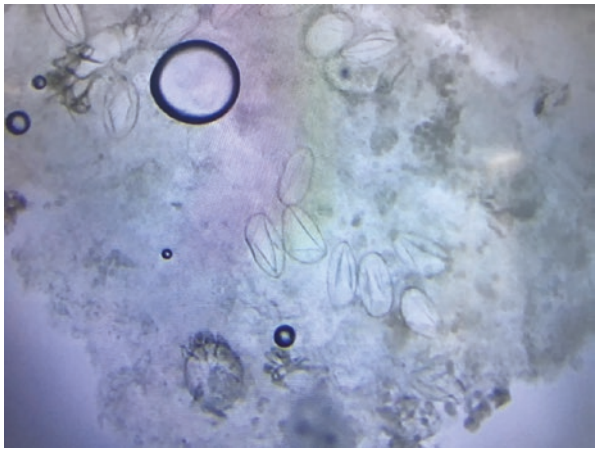

Fig. 17.21 Scabies mite, eggs, faeces

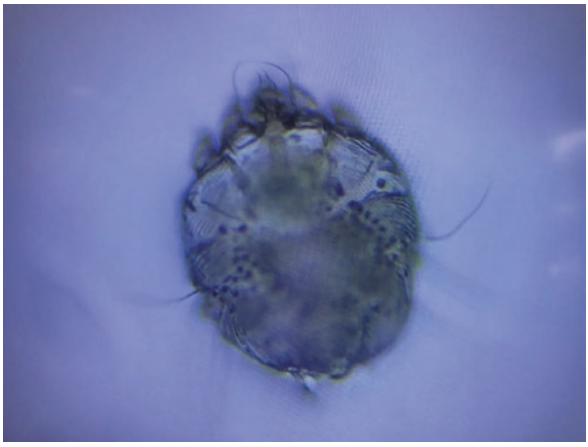

Fig. 17.22 Scabies mite

mineral oil may be applied to the glass microscope slide after scraping. The slide is then examined under low power light microscopy. While visualising a live mite it has 100% specificity, the sensitivity is poor and dependent on the operator collecting the right material from the correct sites. Even when the pretest probability is high, skin scrapings can often fail to confirm the diagnosis because of the low numbers of mites in classic scabies [130]. The greater the number of mites and lesions, the greater the likelihood of successful scraping proving the presence of scabies, and therefore, the yield in severe scabies is considerably higher than mild classic scabies. In crusted scabies, false negatives are highly unlikely if collected from the correct locations; however, they can occur and may occasionally yield only hyperkeratotic debris. Repeated scrapings across multiple sites may be beneficial in cases where highly clinically suspicious on history and/or examination but with a negative initial scrape. Furthermore, serpiginous tracks on microbiological agars are incidental findings that may be observed when sent for culture [51].

Female scabies mites are 0.3 × 0.5 mm in diameter and dwell for the duration of their lives in the distal end of tunnel like burrows 1 to 10 mm where they lay their eggs. The female mites and their burrows are at the limits of unaided visibility to the well-trained naked eye in infestations of classic scabies, whereas male mites are much smaller and usually not visibly detectable [131]. Dermoscopy, *in vivo* epiluminescence microscopy, is a helpful tool in the visualisation of scabies [131, 132]. The anterior portion of the mite and its burrow is demonstrated by the 'delta wing sign', a small brown triangle cephalad to a whitish curvilinear structure reminiscent of a delta-wing jet and its contrail (Fig. 17.23). Dermoscopy in crusted scabies is usually not performed due to obfuscation of burrows by large hyperkeratotic plaques, although may assist in peripheral lesions with papular burrows. In profuse and severe classic scabies, dermoscopy is useful to visualise burrows when they are able to be examined clearly with a dermatoscope operated by trained healthcare personnel. Crusted scabies may show brown irregular structures of burrows constituting the tunnels arranged on top of each other in noodle like patterns [133] and abundant dark brown triangular structures with white structureless wavy lines [106].

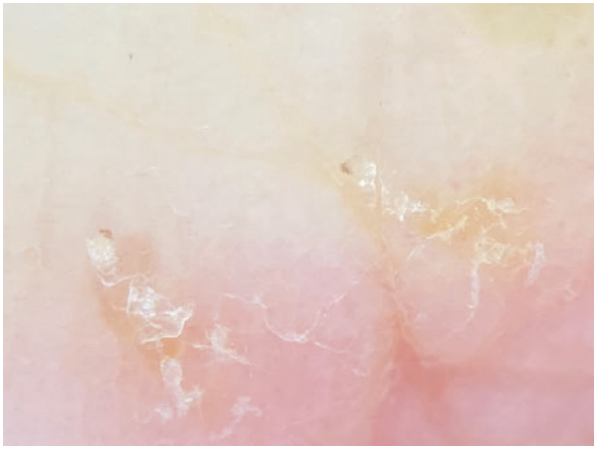

Fig. 17.23 Delta sign with burrows

When appropriately trained, dermoscopy is a useful tool for healthcare workers to diagnose severe classic scabies across many all healthcare environments from community clinics to hospitals through to resource-poor settings, especially when access to alternate diagnostic methods such as confirmatory skin biopsy or specialist expertise diagnosis to exclude other mimics is unavailable. This may be the most sensitive and specific tool available for non-invasive diagnosis, however, it can take an impracticable amount of time, requires training and may be difficult from an infection control perspective in cases where mite burden is high as the face must close to the dermatoscope which must be in contact with the patient (sometime in sites that may cause embarrassment to both the patient and the novice examiner), increasing the risk for unintentional contact with mites on the patient or local fomites [128]. Sensitivity can be variable from as low as 0.11 [11] to as high as 0.83 [131] but improves with disease severity and remains higher than other simple and non-invasive available alternatives such as adhesive tape (0.68) and skin scraping (0.46) in classic scabies. Furthermore, this method is less useful in more richly pigmented skin as well as hair bearing skin [128].

Crusted scabies is easily diagnosed on biopsies of affected skin, although is considered an invasive diagnostic modality. Its greatest utility is in atypical presentations where the diagnosis is unclear and broad differentials are being consideration. Histopathological findings include hyperkeratosis of the stratum corneum with the presence of multiple mites, eggs and faeces; psoriasiform acanthosis and spongiosis of the epidermis; dermal oedema with dilatation of the vasculature; and an inflammatory cell infiltrate consisting of inflammatory $CD8^+$ T lymphocytes and eosinophils [2, 21] (Figs. 17.24a, b and 17.25a–e). While not routinely performed, immunostaining demonstrates a strong positive for IL-1β and TGF-β 1 [2]. The absence of mites on biopsies taken from sites where mites may not be located does not exclude the diagnosis of scabies and may be supported by the aforementioned features found in nearby skin of severe scabies. Superficial shave biopsies may represent an easier alternative, if tissue diagnosis is deemed necessary [109].

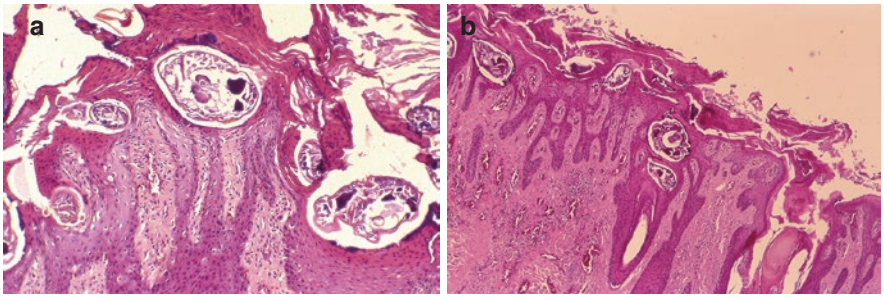

Fig. 17.24 (**a**) Histology high power. (**b**) Histology low power

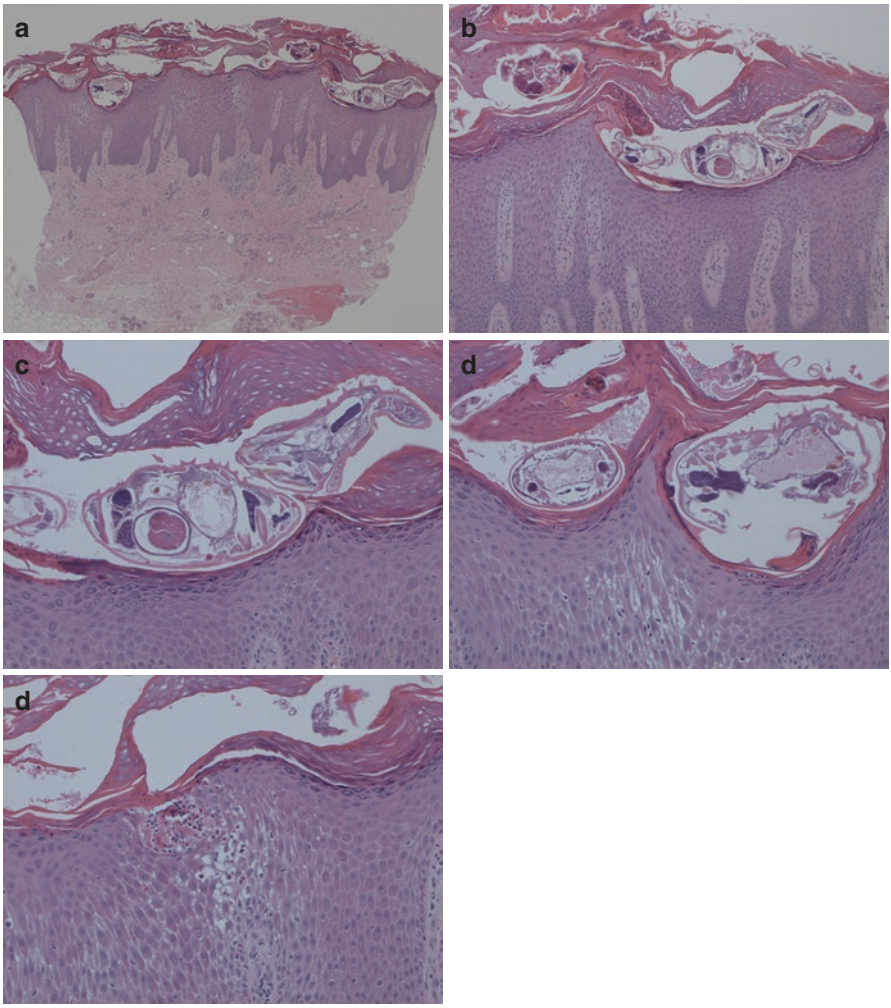

Fig. 17.25 (**a**) Punch biopsy of crusted scabies at scanning objective lens (×4) with numerous visible mites in the stratum corneum and epidermal acanthosis. (**b**) Low power objective lens (×10 magnification) of multiple mites embedded and burrowed into the stratum corneum with serum crusting. (**c**, **d**) ×20 magnification of scabies mites. (**e**) ×20 magnification of eosinophilic spongiosis with mite fragments

Nail clippings and scraping for microscopic examination should be taken in any patients with nail dystrophy, to investigate the diagnosis of crusted scabies, but to also exclude concomitant dermatophyte infection [45].

Healthcare workers, critical to community management in resource-poor settings, can be trained with good diagnostic accuracy in the diagnosis of moderate and severe scabies [134].

17.8 Emerging Confirmatory Diagnostic Methods

Emerging technological advancements in non-invasive diagnosis of scabies are more commonly used for classic scabies and therefore extend to use in severe forms. These tools are not routinely available (beyond research settings) but have advantages for future application including rapid, non-invasive screening and post-therapeutic follow-up, without physical risk [128]. These tools have not undergone extensive rigorous testing in the setting of crusted scabies.

Videodermoscopy allows *in vivo* observation of the skin down to the superficial dermis in real time via a polarised light source of epiluminescence microscopy videography and may provide magnification up to x1000 [128]. Like skin scrapings, adhesive tape and skin biopsy where the presence of the mite confers 100% specificity, videodermoscopy is also specific with the moving round translucent body of the mite and the legs, in addition to the more prominent angulated head seen in high definition. This is quick, non-traumatic and helpful for follow-up, but is expensive and uncommonly used in routine practice [128].

Reflectance confocal microscopy, most commonly used in the identification of melanoma, is an *in vivo* optical imaging modality which allows non-invasive and high-resolution cutaneous imaging that can facilitate identification of the burrow down to the level of the stratum granulosum/spinosum [128]. While being a time-consuming modality that is not routinely available for everyday use, particularly in resource poor settings, it has been shown to be useful in severe classic and crusted scabies to identify, locate and quantify the presence of mites, eggs and faeces as well as specific sites prone to parasitisation [135–137]. A small study was able to confirm the presence of greater than 15 million mites and more than seven million mites in a single person with diffuse erythrodermic crusted scabies, which reinforces the astonishingly severe mite burden and its consequent highly infectious nature [135].

Optical coherence tomography is emerging as a research tool for diagnosis and monitoring of many dermatoses including scabies due to its ability to image the cellular morphology of tissue from the stratum corneum, through the epidermis, and to the papillary dermis including its appendageal structures [128]. It utilises near infrared beams reflected from biological structures to create multiple two dimensional vertical and horizontal images, giving high-resolution confirmatory evidence of the presence of the sharply marginated mass of the mite beneath the stratum corneum [128]. In situ diagnosis of scabies by handheld digital microscopy has been demonstrated to be an accurate modality in a proof of principle study in darkly pigmented Indigenous patients in resource poor environments, but is also not routinely used or available [129].

Polymerase chain reaction is a specific test that could confirm the diagnosis of scabies with high specificity but would rely on expertise in skin scraping sampling [138]. This is not yet routinely available beyond research settings and is not commercially available for use as it is not yet validated [130]. Likewise, a scabies antibody specific enzyme linked immunosorbent assay is under investigation but is not yet available [128, 130].

17.9 Supportive of Severe and Crusted Scabies

In cases where the diagnosis is uncertain, additional features may support a diagnosis of severe or crusted scabies and can include high total immunoglobulins (especially E, G, A) [20], and the presence of a peripheral eosinophilia, although not mandatory, is commonly observed.

In terms of haematological findings, eosinophilia is the most common and well recognised change associated with parasitic infestations. In the largest observational study of crusted scabies, 58% had a prominent eosinophilia reaching as high as $13.0 \times 10\ L^{-1}$, with 12% of patients demonstrating eosinophil counts greater than ten times the upper limit of normal ($7.0 \times 10\ L^{-1}$) [20]. It is notable that while the local milieu of inflammatory cells change in locally affected skin tissue, notably a disproportionate overrepresentation of $CD8^+$ T lymphocytes in lesional skin, peripheral T & B lymphocyte levels are normal (including T-cell subsets) [7]. Extremely high levels of total IgE (96%), IgG (96%) and IgA (64%) are commonly found, with the IgE levels being greater than ten times the upper limit of normal in 73% of crusted scabies in this large cohort study, with a median level of 1700 μg/L and reaching as high as 217,260 μg/L (RR $\leq$ 100 μg/L). IgG levels are also high, and IgG1, IgG3 and IgG4 subclasses are raised; however, these are not routinely performed in systemic work up for pruritic dermatoses including scabies. In research settings, these IgE and IgG subclasses have been shown to be specific to a variety of sarcoptes scabies antigenic proteins [83]. More readily available is radioallergosorbent testing to house dust mite and animal dander, both of which demonstrate cross-reactivity in sensitised individuals [139].

When systemically unwell, markers of acute inflammation are expected in addition to anaemia of chronic disease if the disease course is protracted. It is difficult to attribute all non-specific changes directly to systemic complications of scabies and may represent, at least in part, the underlying disease process that predisposed the patient to severe or crusted scabies. Routine tests that should be considered include screening for comorbid diseases (including HIV, HTLV-1, nutritional screen) as well as investigating for complications. Sexually transmissible infection screening is also recommended in sexually active patients as acquisition of scabies is not uncommon through this modality [26]. Due to the high rates of complications and the duty to diagnose and treat complications early to optimise patient care, diagnostic work up for anyone presenting with suspected crusted or severe scabies should include routine blood work to investigate for haematological, electrolyte, renal complications including systemic markers of acute inflammation; infectious screening to determine bacterial and viral pathogens and speciate them to appropriately target treatment, including blood cultures, bacterial skin swabs, nail clippings and skin scrapings. Enquiries about advanced care planning may need to be considered given the morbidity and mortality faced by patients with this spectrum of conditions.

DIAGNOSIS OF CRUSTED SCABIES: primary diagnosis is most often purely clinical based on examination findings

Confirmative diagnosis

- Skin scraping or nail clippings showing mites, eggs and/or faeces
- Skin biopsy showing mites, eggs and/or faeces in the
  - Stratum corneum along with hyperkeratosis,
  - Acanthosis, eosinophilic and $CD8^+$ T
  - Lymphocyte infiltrate and dermal oedema
- Videodermoscopy
- Dermoscopy
- Burrow ink test
- Reflectance confocal microscopy

Supportive of parasitic infestation

- Eosinophilia
- Elevated IgE
- Elevated total IgG (IgG1, 3 and 4)

Useful to assess baseline and progress with treatment

- Full blood count (anaemia of chronic disease, malnutrition-related anaemia, leucocytosis, eosinophilia)
- Renal function and electrolytes (acute or chronic renal impairment with electrolyte shifts related to impairment of skin integrity)
- Acute phase inflammatory markers

Early identification of common complications

- Bacterial skin swabs, bacterial blood cultures
- Consider viral swabs
- Consider dermatophyte culture

Investigation for contributing comorbidities relevant to the clinical context

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Scabies in Infants and Children

18

Marie-Emeline Marniquet and Sébastien Barbarot

18.1 Type of Lesions

Scabies lesions are a combination of specific and aspecific lesions forming various clinical pictures. They occur about one month after infestation (3–6 weeks) and are due to both the mite and a hypersensitivity reaction to it. Complexity of scabies phenotypes leads to an average diagnostic time of 2 months (Table 18.1) [1]. In order to reduce the diagnostic delay, a good knowledge of the signs of scabies in children is essential.

Authors certify that patients have given permission for publication of clinical photographs.

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Table 18.1 Phenotypes of scabies in infants and children

	Infants	Children	Adolescent
Topography by order of frequency	Ankles and foot Hand and wrists Back Abdomen Arms and forearms Armpits Thigh and groin Knees, knee folds, legs	Hand and wrists Arms and forearms Back Abdomen Ankles and foot Thigh and groin	Hand and wrists Arms and forearms Back Abdomen Thigh and groin Buttocks and genital area
Type of lesions by order of frequency	Vesicles, burrows Nodules Blisters	Burrows Vesicles Nodules Blisters	Burrows Vesicles Nodules Blisters

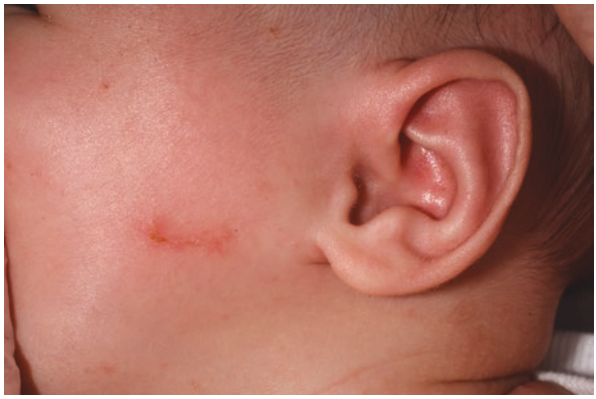

Fig. 18.1 Burrow on the cheek of an infant. (Courtesy of Dr. Hélène Aubert)

18.1.1 Specific Lesions

18.1.1.1 Burrows

Burrows are pathognomonic lesions of scabies found in almost 80% of patients regardless of their age (infants, children and adolescents) [1]. There are short, linear or curved tracks with tiny vesicles at the distal end containing the mite (Figs. 18.1, 18.2, 18.3, and 18.4).

Dermoscopy, a non-invasive optical magnifying technique, reveals the 'delta sign'. The 'delta sign' is a small brown triangular structure corresponding to the pigmented anterior part of the mite followed by the tunnels of the mite. Hands, arms and abdomen are preferential locations for finding mites on dermoscopy [2]. In infants, palms, soles as well as dorsum of the forefoot are commonly involved. Further, severity of the scabies and short duration of the scabies seem to be linked with a higher sensitivity of dermoscopy [2, 3]. There are gaps between studies

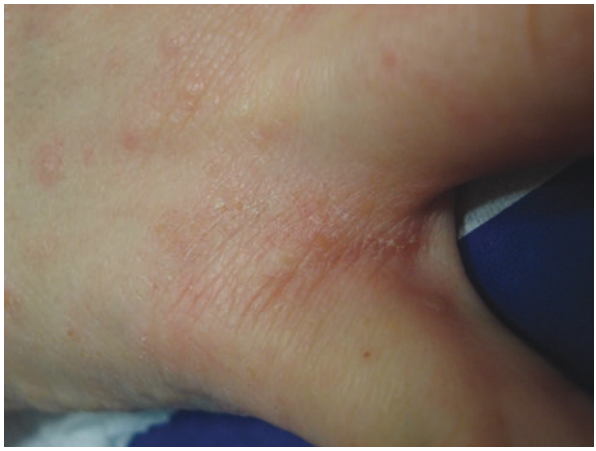

Fig. 18.2 Burrow in an interdigital space in a children. (Courtesy of Dr. Juliette Miquel)

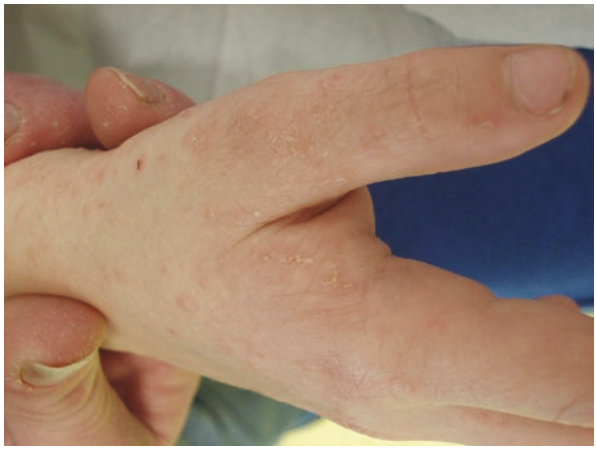

Fig. 18.3 Burrows in children's hand. (Courtesy of Dr. Juliette Miquel)

Fig. 18.4 Burrow in a child's dark skin. (Courtesy of Dr. Hélène Aubert)

regarding sensitivity and specificity of this technique, although it was reported to be at least as good as microscopic examination [2–5]. Further, even if performed by beginners, dermoscopy shows high sensitivity and low specificity which makes it a good screening test [2]. Dermoscopic visualization of the mite on dermoscopy allows the accurate diagnosis of scabies following the 2020 consensus criteria of the International Alliance for the control of scabies [6]. In addition to its diagnostic value, dermoscopy can also be useful for treatment monitoring. The absence of detection on dermoscopy features the "delta sign" reflecting a successful treatment of scabies.

18.1.1.2 Nodules

Nodules are red or purple, itchy and sometimes excoriated. They can be isolated or multiple (Fig. 18.5). Preferential locations for nodules are large folds like axillae or genitalia, sometimes unilateral (Fig. 18.6). They are more frequent before 2 years old (63%) [1]. Nodules correspond to granulomatous reactions to dead mite antigens or intradermal passage of live mites in infants with thinner epidermis.

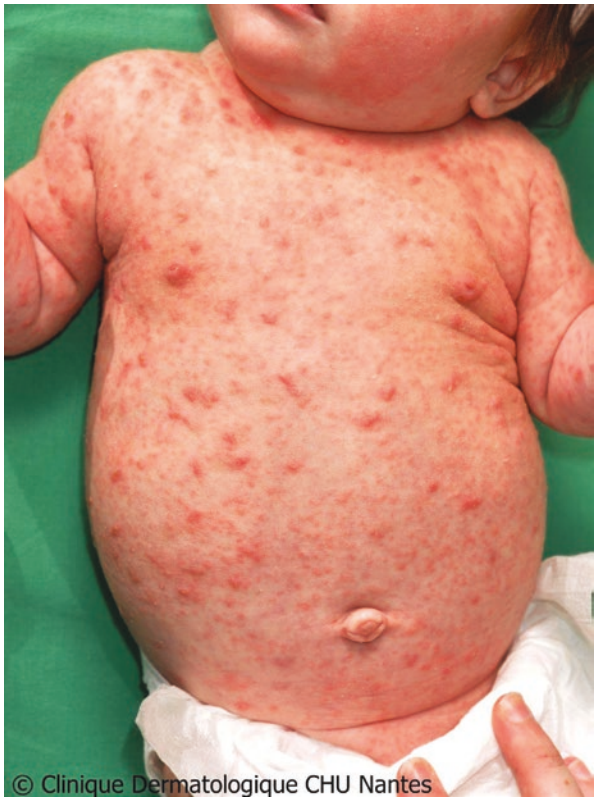

Fig. 18.5 Multiple nodules in an infant. (Courtesy of Dr. Hélène Aubert)

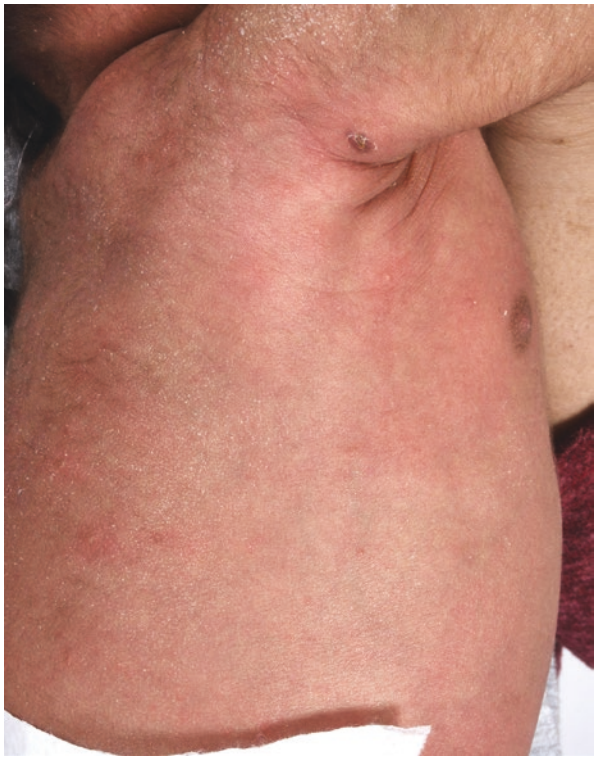

Fig. 18.6 Scabious nodules on the axillae in an infant. (Courtesy of Dr. Hélène Aubert)

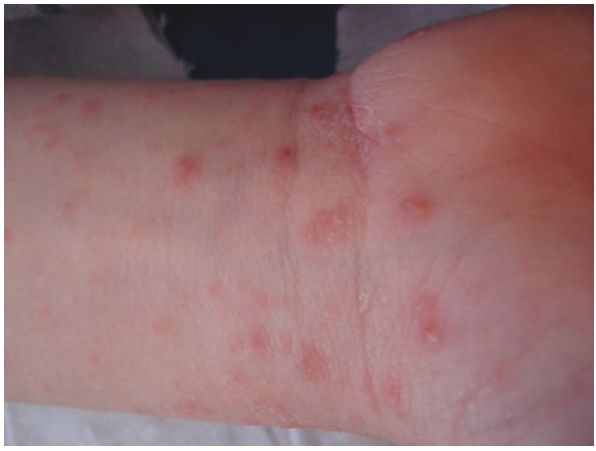

Fig. 18.7 Burrows and pustule on a children's wrist. (Courtesy of Dr. Juliette Miquel)

18.1.1.3 Vesicles or Pustules

Vesicles and pustules are more frequently observed in infants and children (Figs. 18.7, 18.8, 18.9, and 18.13) [1]. One study reports that scabies account for 6% of diagnosis among pustular rashes in infants [7]. They are found mostly on the soles and palms or in interdigital space.

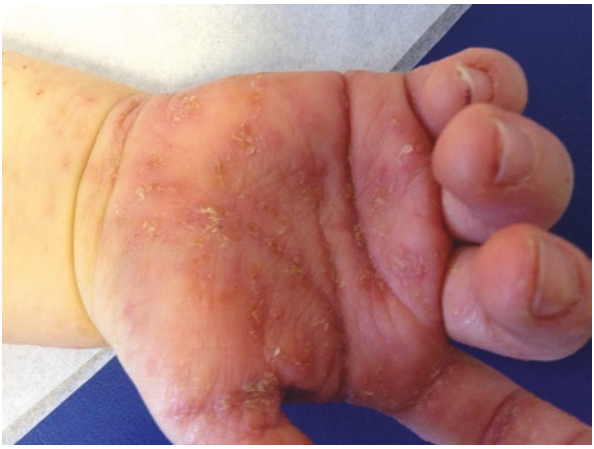

Fig. 18.8 Palmar pustules in a children. (Courtesy of Dr. Hélène Aubert)

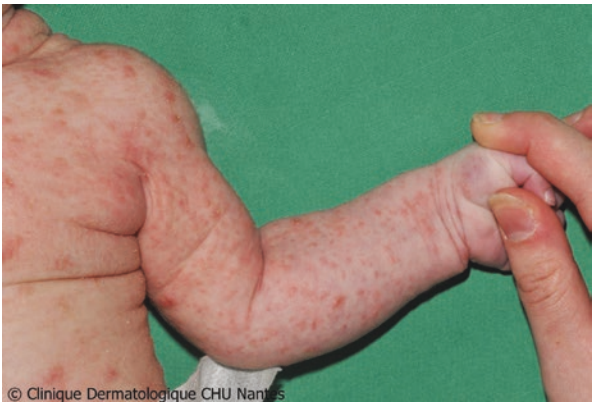

Fig. 18.9 Vesicles and scabious nodules in an infant (Courtesy of Dr. Hélène Aubert)

18.1.2 Non-Specific Lesions

The clinical presentation is polymorphic, and other nonspecific lesions are found lateral to pruritus. Indeed, pruritus leads to eczematous reaction (type IV); thus, excoriation, crusts, prurigo and even lichenification are commonly observed in children (Fig. 18.10). This may lead to misdiagnosis if not associated with characteristic lesions.

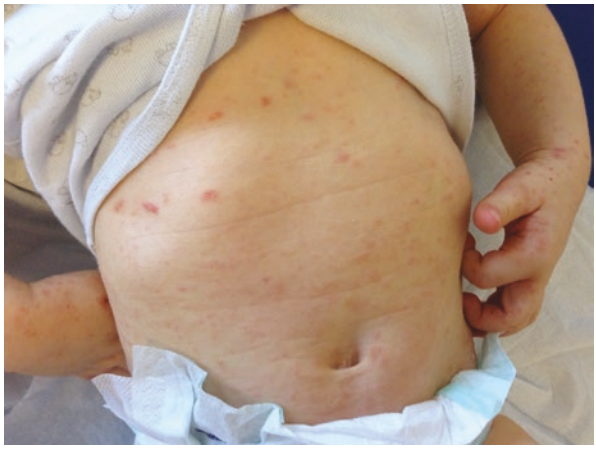

Fig. 18.10 Pruritus eczematiform rash and scabious nodules in children. (Courtesy of Dr. Hélène Aubert)

18.2 Topography

A specific topography is associated with scabies in children. Those locations were investigated in a cohort of 323 children that found lesions, in children under 15 years of age preferentially on the face, ankles, foot, soles, head and neck, and scalp (Fig. 18.1) [1]. Soles and scalp were even more involved under 2 years old.

Facial involvement is found with an increased gradient according to age [1]. Facial involvement of the infant could be related to affected nipples of the mother.

In adults, involvement of the back is rare [8] and can be found when patients are bedridden for long periods. In children, this location is common and can be found in up to 71% of children [1].

Involvement of lower limbs (including foot, ankle, knee and leg area) follows as well an increasing gradient according to age [1]. Palmoplantar involvement is more common in infants and young children [9]. And more precisely, soles are more frequently involved than palms in infants and children [1]. Dorsum of the forefoot is also frequently involved in infants.

Nails may represent a reservoir of mites. In a cohort of 47 children with confirmed scabies, three cases had sarcoptes mites revealed by dermoscopy or microscopy (6.4%) [10]. The nail damage consisted of hyperkeratosis, onycholysis, onychoschizia and pachyonychia. It is mostly found in hyperkeratotic forms of scabies, but can also be in common scabies. Nails can be completely normal which explains the likely underdiagnosis of nail scabies. Preferential locations are toenails and thumbnails. It is not only a child's prerogative, as it is also frequently found in adults [8]. Diagnosis can be made by parasitology examination or dermoscopy revealing the subungual presence of scabies with the 'delta sign'. As this location is probably secondary to pruritus, prevention involves cutting, brushing the nails and applying anti-scabies topicals under the nails when treating every common scabies (with or without clinical nail involvement). Chemical avulsion of the nail and

repeated applications of anti-scabies to the nail bed are proposed. Ungual availability of ivermectin is suspected but not confirmed.

18.3 Associated Symptoms

18.3.1 Pruritus

Pruritus is absent in 10% of infants (versus 3% of adolescents). One reason for this is that this reflex is not acquired yet. If present, it can be expressed by irritability, wriggling when undressing, rubbing of the feet, sleep disorders and even a break in the weight curve (Fig. 18.10). Pruritus is severe in 48% of infants (versus 72% of adolescents). It is predominantly nocturnal in 1/3 of them (versus 54% of adolescents). However, 20% of infants and children had mainly daytime pruritus.

18.3.2 Familial Pruritus

Half of the time, the infant's involvement is the most severe and profuse. If absent, it should not rule out the diagnosis.

18.4 Atypical Presentation of Scabies

18.4.1 Crusted Scabies, Norwegian Scabies

Crusted scabies is characterized by hyperkeratosis and crusting of the skin. This is the result of profuse mite proliferation: several millions of sarcoptes [11]. This occurs in immunodeficient patients due to T-cell immune response deficiency as in immunodeficiency (HIV, haemopathy, congenital T-cell immunodeficiency and chronic mucocutaneous candidiasis) [12, 13] or patient on immunosuppressive treatments (systemic or topical) [14–16]. Since children are more likely to have atopic dermatitis, topical steroids could be easily applied on them leading to more severe scabies. This may also be related to motor or sensory deficiency, or mental retardation because of the inability to scratch, which would prevent the elimination of a number of sarcoptes [17, 18].

18.4.2 Bullous Scabies

Bullous scabies (BS) is rare and independent of age (more in elderly). About 20 cases have been reported so far in infants and children: from 6 months to 15 years old. Locations of bullous lesions are hands and in the genital folds but can also be generalized. Boralevi et al. reported that 6.2% patients of scabies (12 out of 193) below 15 years presented blisters, implying that BS may have been largely misdiagnosed or neglected [1]. Bullous lesions may develop concurrently with, or after, the

occurrence of scabietic lesions. Histologic findings are sub-epidermal splits with variable infiltrate, eosinophilic spongiosis or both [19]. Direct immunofluorescence showed linear C3 alone or in combination with various immunoglobulins at the dermoepidermal junction [19]. The mechanism of bullae formation is unclear, and hypothesis is plural: type 1 hypersensitivity reaction to mites, autoantibody-mediated bullae formation, autoeczematization, direct injury or secretion of lytic enzymes by the scabies mites and superinfection of scabies lesions with *Staphylococcus aureus* [20]. Differential diagnosis in children could be bullous impetigo, epidermolysis bullosa, papular urticaria and autoimmune blistering disease. Presumptive treatment may be tried to confirm the diagnosis of BS [21]

18.5 Complications

18.5.1 Superinfection

Prevalence of superinfection of scabies is substantially higher in children than in adolescents and adults. Impetigo is common, particularly in children, with the highest prevalence in Australian Aboriginal communities (49·0%) [22]. Superinfection is mostly due to *Staphylococcus aureus* and *Streptococcus pyogenes* [23]. These complications range from local skin and soft tissue infections, including skin abscesses, cellulitis and necrotising fasciitis, through to septicaemia, renal disease and potentially rheumatic heart disease [23].

18.5.2 Relapse and Recurrent Episodes

Relapse is not rare, as it was observed in 55% of infants and 66% of children. Hypothesis would be that treatment failure of scabies is due to reductance by parents to treat scalp and face with topical treatment, absence of nail treatment, under-treatment of the environment and close contacts.

Recurrent episodes are common, especially in children, since infestation does not confer complete immunity and protection on further exposure [24].

18.6 Differential Diagnosis: 'Scabies Incognito'

Atypical scabies phenotype may occur when long-standing infestations use topical corticosteroid.

18.6.1 Atopic Dermatitis

Scabies can easily mimic atopic dermatitis (AD) with eczematization of scabies lesions (Fig. 18.11). The Williams criteria are not discriminating in establishing the differential diagnosis [25].

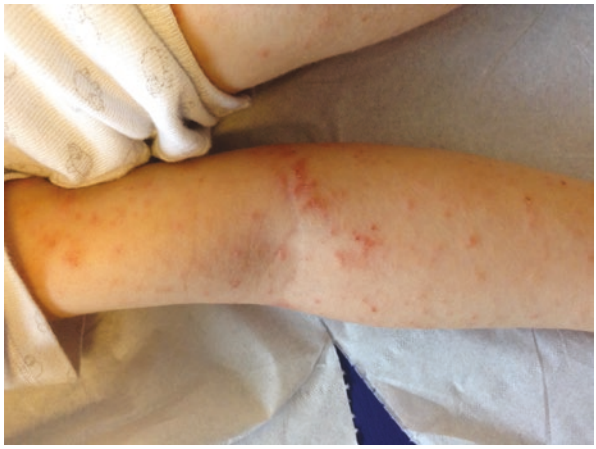

Fig. 18.11 Eczematiform rash in children. (Courtesy of Dr. Hélène Aubert)

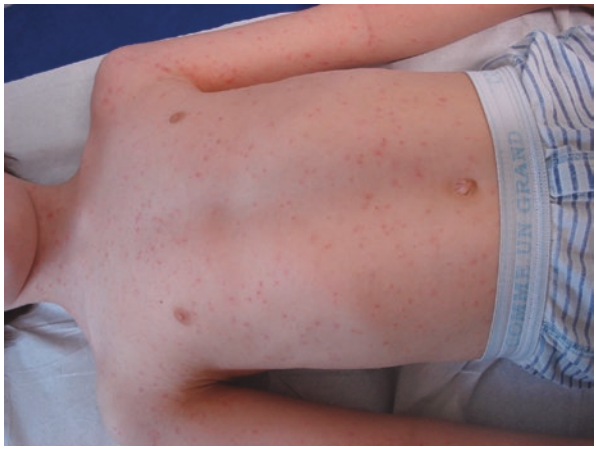

Fig. 18.12 Prurigo strophulus like eruption. (Courtesy of Dr. Juliette Miquel)

18.6.2 Cutaneous Mastocytosis

Before 1 years old, cutaneous mastocytosis presents with itchy papules or nodules red, brown or purple. Darier's sign may be falsely positive in scabies [26, 27]. Biopsy can be helpful, although an increased number of mast cells in scabietic nodules may hinder the diagnosis.

18.6.3 Papular Urticaria and Prurigo Strophulus

Papular urticaria, also known as skeeter syndrome, consists of a persistent insect bite reaction, typically itchy red papules or vesicles in children lasting days or weeks. However, lesions are more localized and monomorphic. Prurigo strophulus-like reactions can also be mistaken (Fig. 18.12).

18.6.4 Langerhans Cell Histiocytosis

Langerhans cell histiocytosis presents as widespread eruption of papules, vesicles and excoriations that can have a petechial component. It is mostly monomorphous rashes. The inflammatory cell infiltrate in *Sarcoptes scabiei* infestations often includes Langerhans cells. Thus, childhood scabies can be confused clinically and histopathologically with Langerhans cell histiocytosis [28–30].

18.6.5 Infantile Acropustulosis

Infantile acropustulosis (IA) is a self-limited, recurrent, pruritic disease affecting acral surfaces of young children. It may mimic scabies due to the presence of acral vesiculopustular lesions in both conditions. However, IA usually occurs after infestation with *Sarcoptes scabiei* [31, 32] (Fig. 18.13).

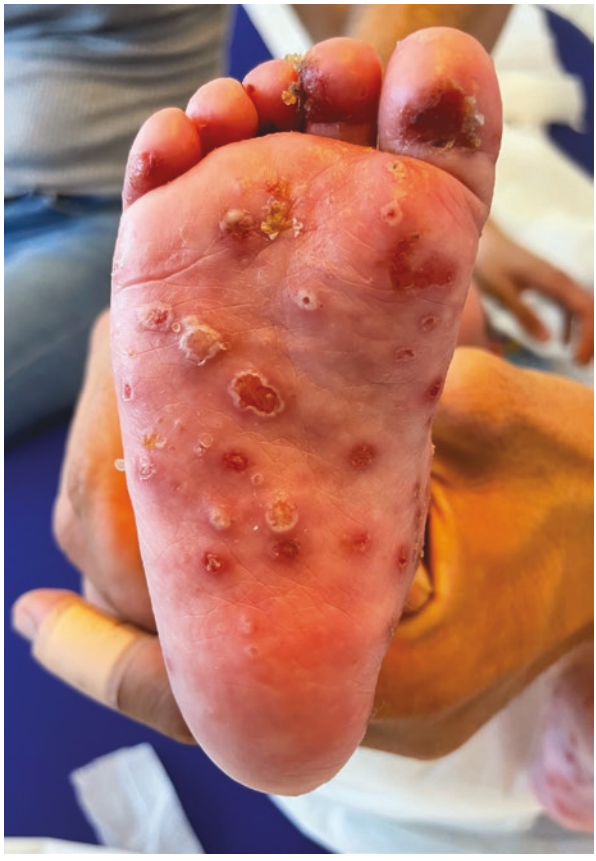

Fig. 18.13 Plantar acropustulosis associated with scabies. (Courtesy of Dr. Marie-Emeline Marniquet)

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Parasitological Diagnosis of Scabies

19

Françoise Foulet and Françoise Botterel

19.1 Introduction

Human scabies is a frequent, cosmopolitan, itchy and contagious ectoparasitosis caused by a mite, *Sarcoptes scabiei* var. *hominis*. Consensus criteria for diagnosis of scabies were recently developed and included three levels of certainty for the diagnosis. Light microscopy of skin samples is the gold standard for confirmed scabies (A1) [1]. Sampling consists of scraping the burrows, vesicles and nodules to collect parasitic material for examination under light microscopy. The diagnosis of scabies will be confirmed by showing adult sarcoptes, eggs and/or mite faecal pellets (scybala).

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K. Fischer, O. Chosidow (eds.), *Scabies*,
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Table 19.1 Videodermoscopic signs of live and dead mites

Life mites	Dead mites
Movements of head and legs, motility of intestinal peristalsis	Absence of any movement of structures or intestinal peristalsis
Different position of the mite at 24- to 48-h intervals	Degradation of the mite, which is characterised by changing of the dark 'delta wing' to a translucent structure of the head and legs. This resembles a 'dry hydrangea'

Nevertheless, parasitic sampling can be faulted; indeed, the parasite density varies according to the clinical form and the evolution over time. In the first 2 to 3 weeks corresponding to the incubation phase, clinical lesions are lacking. An itchy sensation may exist, especially if there is a notion of contagion. In this case, parasitological sampling and dermoscopy are faulty. In the weeks following the onset of lesions, patients may be pauciparasitic and the sample may be negative even if the biologist is experienced. In contrast, the crusts contain thousands of sarcoptes in profuse crusted scabies.

Sampling can be painful, particularly in children or in adults for certain locations, such as genital nodules in men.

For these reasons, dermoscopy, which is non-invasive, painless and easy to use, is tending to replace scratching [2]. More expensive and less easy to use, confocal microscopy visualises the parasites and their viability (Table 19.1) [3].

In cases where sampling or dermoscopy are not feasible, the diagnosis can be clinical based on the topography and appearance of the lesions, the notion of itching in the entourage and the notion of insomnia itching [4, 5].

19.2 Clinical Lesions

19.2.1 Evocative Clinical Signs

Clinical knowledge is essential for the biologist in order to collect specific lesions. The lesions are usually located on the anterior part of the body and the patient present with pruritus and often insomnia. Skin lesion such as papules, urticarial lesions, eczematisation and scratching lesions are the consequences of the immune reaction against the mite antigens [6]. Nevertheless, no parasite is found in these lesions.

19.2.2 Specific Lesions in Common Scabies

1. *Mite burrows:* At the time of infection, the adult males and females are on the epidermal surface and then the fecundated females will migrate under the skin and form a burrow in which they will deposit their eggs. The burrows are sinuous

and greyish in colour if hygiene is poor and measure up to 1 cm. They are mainly on the wrists and interdigital spaces but can appear on the nipples in women and on the palms and soles, even on the back in infants. The scraping the entire length of the burrow allows the observation of larvae, adult parasites, eggs and faecal pellets. Dermatoscopy allows the burrow to be followed and the sarcoptes to be seen, which may be 'V' shaped, sometimes described as a 'jet-with-contrail' sign.

2. *Vesicles:* They are Pearly colour (pearly vesicle) at one end of the burrow. It contains the adult female.

   In infants, vesicles and burrows have a preferential palmoplantar localisation.

3. *Nodules:* The nodules are related to an inflammatory reaction of the organism around the living parasite (scabious nodule) or dead parasite (post-scabious nodule). The nodules measure from a few millimetres to 1 cm. The sampling is painful because it must be done in depth to recover the parasite. Nodules occur preferentially in the genitals in men and in the armpits and nipples in women.

19.2.3 Specific Lesions in Crusted Scabies

In profuse crusted scabies, erythroderma is observed with crusted lesions that may occur over the entire body. The face and scalp are frequently affected. In these lesions, all stages of parasites are present.

19.3 Samples

19.3.1 Scratching Method

The sample must be taken with gloves, or even with an overblouse in the case of highly contagious scabies. In common scabies, patients are pauciparasitic, and many lesions have to be analysed before giving a negative answer on the samples. Due to the low sensitivity of the samples, it is recommended to repeat them in case of strong clinical suspicion (Table 19.2). The examiner can use a dye to apply directly to the skin (Indian ink) to improve the visibility of the burrows. The lesions are opened and scraped using a vaccinostyle (Fig. 19.1), a scalpel or a Vidal curette. The curette can also be impregnated with immersion oil to trap the scraping product obtained from scabietic papules or from under the fingernails, according the scabies clinical form (common or crusted scabies).

In crusted scabies, because of the abundance of mites, the diagnosis is easier. For sampling, only one scraping product from the crusted lesion is sufficient. In this scabies form, sub-nail scrapings can be added to the diagnosis procedure.

Table 19.2 Comparison of the specificity and sensitivity of the different currently available non-invasive diagnostic methods for scabies

	Clinical diagnosis algorithm	Skin scraping and light microscopy	Burrow ink test	Adhesive tape test	Epiluminescence microscopy (dermoscopy)	Video dermatoscopy	Reflectance confocal microscopy (RCM)	PCR-based method
References	[7]	[8, 9]	[10]	[9]	[8, 9]	[11]	[11]	[12, 13]
Sensitivity (%)	96.2	90/46	36.6	68	91/83	95	92	75.7/37.9
Specificity (%)	98	100/100	100	100	86/46	97	100	100/100
Positive predictive value (%)	87.7	100/100	–	100	88/47	97	100	–/100
Negative predictive value (%)	99.4	90/77	–	85	90/85	95	92	–/61.7
Visualised structures	–	Burrow, mite, eggs, larvae, faecal pellets	Burrow, mite, eggs, larvae, faecal pellets	Burrow, mite, eggs, larvae, faecal pellets	Burrow	Burrow, mite, eggs, larvae, faecal pellets	Burrow, mite, eggs, larvae, faecal pellets	–
Duration of the procedure	15 min	30 min	5 min	10 min	5–10 min	5–10 min	60 s to 10 min (each lesion)	Several hours

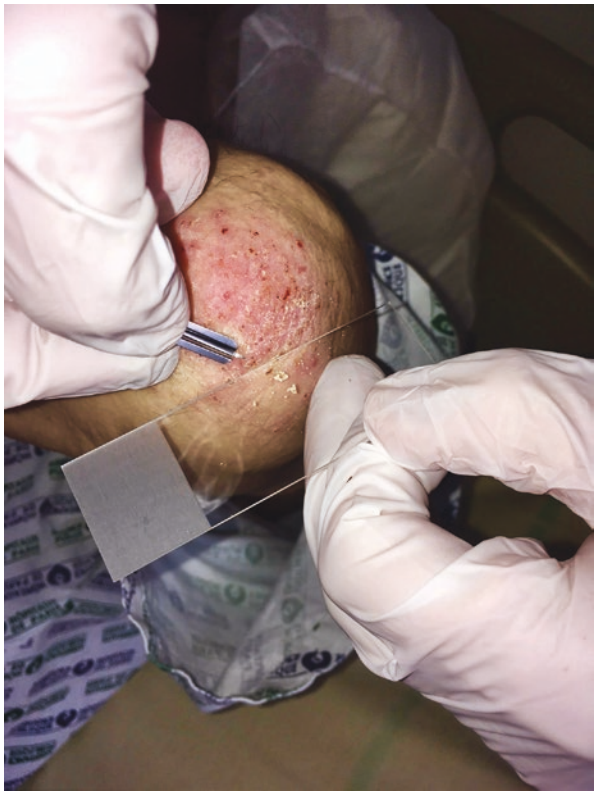

Fig. 19.1 Scratching method with a vaccinostyle

19.3.2 Adhesive Skin Cellophane Method

This method consists of applying an adhesive strip to evocative lesions after surface scraping of the skin, then transfer to a slide and observation in light microscopy between blade and coverslip with or without colouring or lightening. This easy and quick technique is not recommended in common scabies, but it can be used for hyperkeratotic scabies in which crusts are abundant with adult sarcoptes, nymphs, eggs and faecal pellets.

19.3.3 Identification with Light Microscopy

Squamous and serosity from the sample are placed on a slide in a drop of lactophenol, in 10% of KOH or physiological saline. This product is then placed in a drop of immersion oil which is covered with a coverslip. The scraping products are examined between slide and coverslip with an optical microscope (MO) at low magnification (×10). The diagnosis is based on identifying adults' mites, nymphs, eggs or faecal pellets (Fig. 19.2).

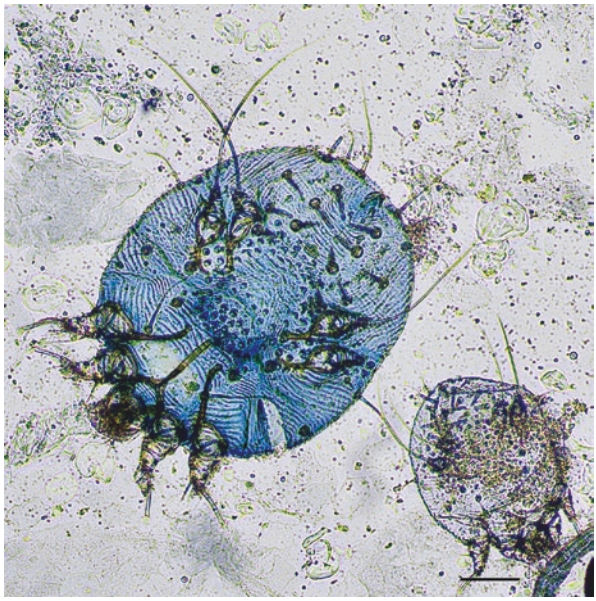

Fig. 19.2 Scabies mite and larvae. Magnification ×100. Scale 30 µm

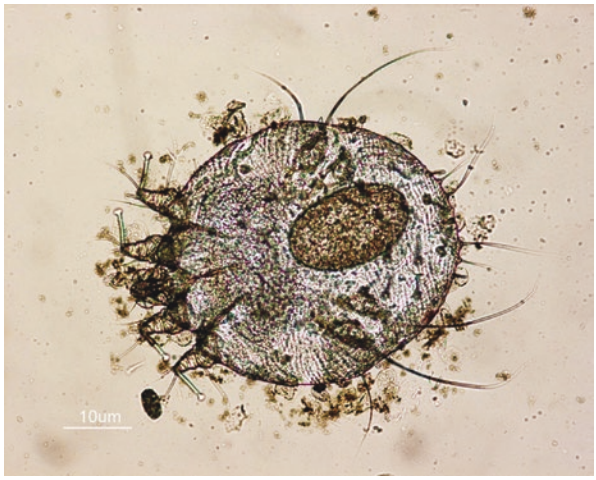

Fig. 19.3 Female scabies mite with eggs, taken from skin scraping. Magnification ×100

The adult mite has four pairs of legs and is globular in shape, with no segmentation between the head, thorax and abdomen, unlike insects. The female size is 300 µm to 500 µm long by 230–420 µm wide; the male and nymphs are shorter. As all *Acarus* genus, nymphs and adults have eight legs (six for the larvae), the two front pairs, facing forward, end with suckers. The posterior pairs end in long setae. On the dorsal surface of the mite, transversally arranged thorns and ten pairs of spines arranged on two sides are observed (Fig. 19.3).

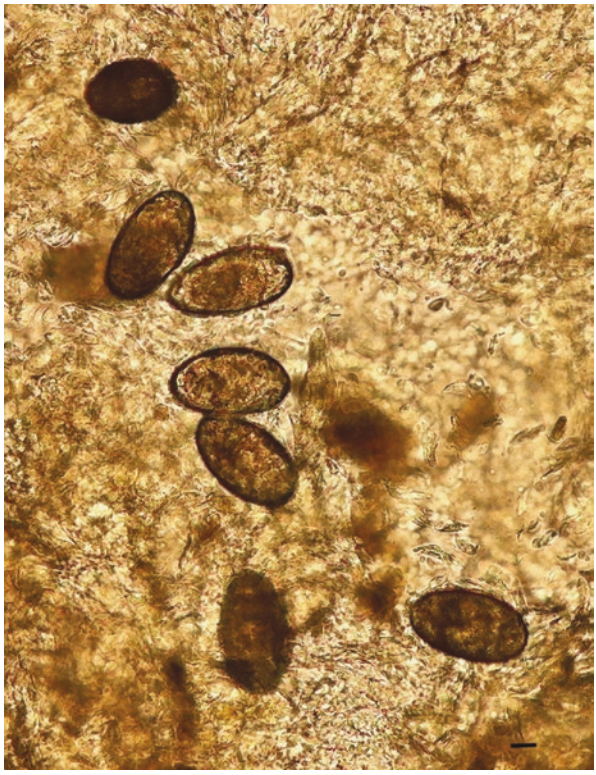

Fig. 19.4 Eggs ($n = 7$) with larvae inside. Magnification ×100. Scale 30 µm

Eggs measure 100 to 150 µm, and in the latter part of the development, the larva lies in the egg in a characteristic position with legs bent in over the ventral surface. Empty eggs or eggshell fragments can be observed (Fig. 19.4).

19.4 Indirect Methods

A hypereosinophilia (>0.5 G/L) on the blood count can be observed in profuse scabies.

To date, serological techniques with the detection of antibodies against *Sarcoptes* have no place in the diagnostic tools of scabies in humans. Enzyme immunoassay techniques are currently being developed, particularly in the context of animal scabies, and will be analysed in another part of this book.

19.5 Conclusion

Parasitological samples, due to their low sensitivity, are only of value if they are positive. Their negativity should not exclude the diagnosis of scabies. These different tools are summarised with their sensibility and specificity (Table 19.2). The experience of the examiners increases the sensitivity of the parasitological diagnosis. Other less invasive and non-operator-dependent techniques are developing, such as dermoscopy and even confocal microscopy, which allow the parasite and the eggs to be visualised more easily. The latter is developed in other chapters of this book.

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Diagnosis of Scabies in Settings with Good Health Infrastructure

20

Regina Fölster-Holst and Cord Sunderkötter

20.1 Introduction

Scabies shows great diversity with regard to its different clinical manifestatiosn as well as to its response to antiparasitic therapy. A special aspect is the patient's immune status, which is not only influenced by age, but also by the patient's underlying diseases and medication.

In countries with an underdeveloped health system, scabies, including severe forms such as crusted scabies, is certainly more common than in industrialised countries. However, Germany has also experienced a renaissance of scabies in the last 5 years, which is particularly evident in the increased number of patients in the outpatient departments of dermatological clinics, in hospital admissions, and the increased prescriptions of scabicidal drugs. However, there is no exact prevalence analysis in Germany, since it is not a notifiable disease. In addition, false-positive diagnoses (made without the confirmatory detection of mites and/or eggs and/or faeces by light microscopic or dermoscopic analysis) and multiple therapies of a single patient are incorrectly included in the total number of patients with scabies [1, 2]. In the following, we will focus on minimal forms of scabies ('Scabies discreta') and atypical forms that imitate other dermatoses ('Scabies incognito') as well as special diagnostic measures.

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20.2 "Scabies Incognito" and "Scabies Discreta" ("Well-Groomed Scabies")

In some patients who practice excessive washing and bathing procedures, hardly any skin changes of scabies can be seen. However, they describe pronounced itching. It is then recommended to take another close look at typical sites of predilection, such as the genitals and the nipple area of the mammae, since skin changes suspected of being scabies such as mite burrows and scratched papules are to be suspected at these locations [3].

Scabies is known to provoke a cell-mediated hypersensitivity to mites, their eggs and faeces leading to eczematous inflammation of the skin. The inflammation and the related pruritus will be reduced by using anti-inflammatory drugs such as topical or systemic corticosteroids. In such cases, typical symptoms including pruritus and inflammation may largely disappear; however, the scabies infestation still exists and the patient is still contagious.

Stiff and Cohen [4] described a 59-year-old African male patient presenting with papulosquamous plaques on the torso, resembling lesions of pityriasis rosea. Complete examination of the skin demonstrated scaly burrows on his finger webs, which showed mites and their faeces and eggs in a microscopic analysis.

Cohen [5] showed also scabies surrepticius in an adult patient with pruritic blisters and urticarial plaques resembling bullous pemphigoid (BP) (since the direct immunofluorescence revealed findings of BP, it cannot be excluded as an additionally underlying disease).

A Turkish patient published by Karaca et al. [6] showed subcorneal pustular dermatitis-like eruptions.

20.3 Diagnostic Measurements

The initial suspicion of a diagnosis of scabies is mainly made on clinical signs including serpiginous burrows and distribution of the skin lesions. In addition, intense pruritus, worsening at night and contact to affected persons in the near vicinity are hallmarks of diagnostic features. To verify the diagnosis, finding the mites and/or their eggs and faeces is required. For this, there are different diagnostic measurements available including dermoscopy and microscopic analysis using adhesive tape test or skin scraping. Walter et al. [7] compared these diagnostic properties in a prospective evaluator-blinded study in a resource-poor setting. They found that the sensitivity of dermoscopy was significantly higher than the sensitivity of the adhesive tape test and stated that dermoscopy is a valid tool for diagnosing scabies in a resource-poor setting if trained personnel are available. The adhesive tape test is recommended for screening purposes because it is easy to perform and shows high positive and negative predictive values, whereas skin scraping cannot be recommended as a diagnostic tool in this setting.

Park et al. [8] stated that skin scraping with dermoscopy is a suitable diagnostic measurement, even in patients with a history of previous steroid treatment (scabies

incognito). In the absence of dermoscopy or microscopy, they recommend for searching visible burrows as reliable positive marker of scabies. Yet, Lallas et al. [9] described a patient with scabies lesions on the face and neck, which was misdiagnosed during sequential visits. Only when dermoscopy was applied, the diagnosis of scabies was made.

In 2018, Engelman et al. [10] and the International Alliance for the Control of Scabies (IACS) established consensus criteria for the diagnosis of scabies. They stated three categories of diagnosis:

- *Confirmed scabies* by visualisation of the mite or mite products (eggs, faeces)
- *Clinical scabies* by visualisation of scabies burrows or typical lesions affected male genitalia or typical lesions in typical distribution and two history features
- *Suspected scabies* by visualisation of typical lesions in a typical distribution and one history feature or atypical lesions or atypical distribution and two history features.

Burrows, mites and their products (faeces, eggs) can be visible by using dermoscopy, which is very sensitive and specific diagnostic feature. Mang and colleagues [11] studied the disease activity of scabies using videodermoscopy. In their clinical letter, they show very impressive figures, which distinguish live from dead mites, albeit in higher magnifications than dermatoscopes usually provide. This non-invasive diagnostic measurement also enables assessment of therapeutic effects which currently appears to be more and more important in consideration of emerging scabies resistance to current therapeutics.

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Diagnosis of Scabies in Resource-Poor Settings

21

Michael Marks

Scabies is one of the commonest infections, and one of the commonest dermatoses that a health care provider will encounter when working in resource-poor settings [1]. As such, an understanding of how to diagnose scabies is essential for clinicians working in low and middle income countries (LMICS). A related issue is the diagnosis of impetigo which frequently complicates scabies infestation in LMICs.

As in high-income settings (addressed in Chap. 15), clinical examination and history taking are central to the diagnosis of scabies. In most low-income settings, there is an absence of highly trained health care workers with expertise in skin diseases such as dermatologists and therefore health systems are reliant on mid-level health workers to make the diagnosis. Depending on the setting, these mid-level workers may be referred to by a variety of titles including nurses, physician's assistants, medical officers or clinical officers. Many of these individuals will have had little if any formal training in dermatology or the diagnoses of common skin infections and infestations.

A consequence of the absence of specialists is that the diagnosis of scabies is almost entirely clinical in LMICs with no role for dermatoscopy or direct visualisation of the mite or its eggs outside of research studies. Even in the hands of a dermatologist, the performance of dermatoscopy on darker skin is believed to be reduced, which is further limiting the value of this approach.

In order to assist in the diagnosis of scabies and related bacterial infections a number of groups have developed standardised diagnostic algorithms for use by mid-level health care workers [2, 3]. In areas of high prevalence these standardised approaches have been shown to achieve reasonable levels of both sensitivity and specificity compared to a reference standard clinical examination [3–5]. Mahé et al. developed and assessed an algorithm for the diagnosis of pyoderma, scabies,

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superficial fungal infections and leprosy. The diagnosis of scabies was based on the presence of itching in at least two body sites, with visible lesions in typical lesions for scabies and the presence of others in the same household with itch. Differing combinations of these features were assessed with regards to their sensitivity and specificity. All combinations achieved high specificity (95%). The presence of itch with either lesions in two typical locations or a household member with itch achieved a sensitivity of greater than 95%.

The impact of this training package was subsequently assessed by examining the management of patients presenting to primary care with skin problems in Mali [5]. Following training the knowledge of health care providers in relation to scabies diagnosis increased from 43% at baseline to 88% immediately following the training. A subgroup of participants were followed 18 months after the initial training and their improved level of knowledge had persisted. This was accompanied by an improvement in the clarity of diagnoses recorded in primary health care records and the appropriateness of treatment prescribed for the registered diagnosis.

In a separate study in Fiji, Steer et al. implemented a similar algorithm for the diagnosis of scabies, pyoderma and superficial fungal infections. Scabies was defined as the presence of itchiness and papular lesions whilst infected scabies was defined as the additional presence of lesions with pus or crusts consistent with pyoderma. The algorithm was assessed by comparing the performance of nurses at two clinics with that of a paediatrician. Sensitivity and specificity were both high for infected scabies (89.1% and 88%) but the sensitivity was markedly lower for uninfected scabies (58.3%) [3].

With growing interest in the global health control of scabies [6] there has been increasing interest in standardising the diagnostic approach and criteria used. The International Alliance for the Control of Scabies (IACS) [7] undertook a Delphi process to try and develop standardised criteria that could be used within public health programmes focusing on scabies [8]. The final criteria provide a number of categorisations for scabies diagnosis. Level A consists of criteria for ‘Confirmed Scabies’ referring to a diagnosis made with direct visualisation of the mite or its products. Given the absence of appropriately trained individuals, limited resources and the poor sensitivity of these approaches this component of the delphi criteria is unlikely to be used in resource poor-settings outside of specialist centres or research studies.

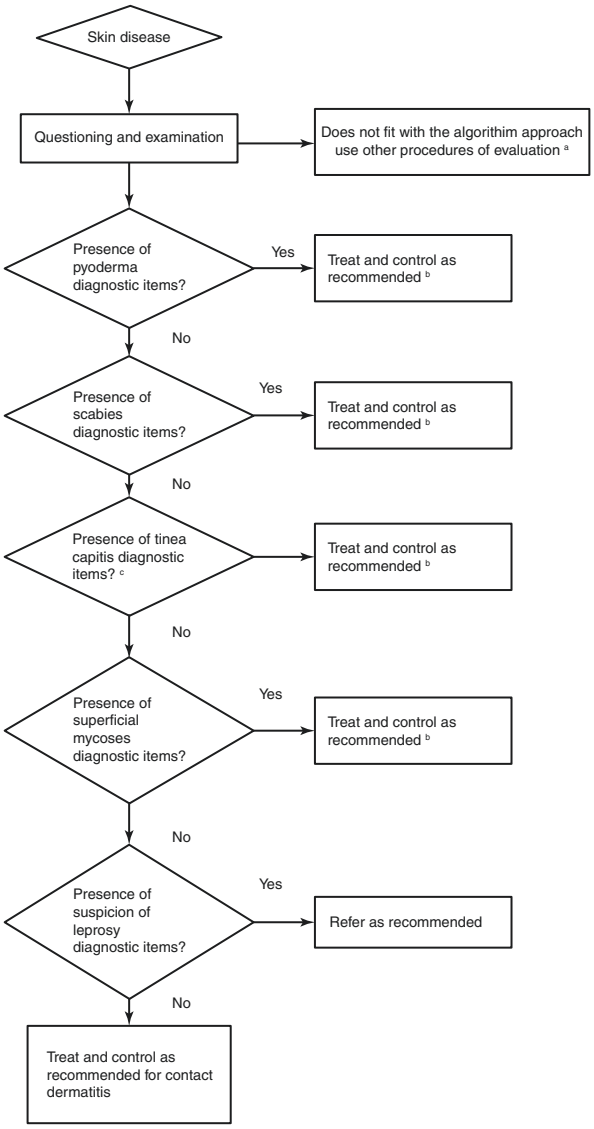
Level B or ‘Clinical Scabies’ is divided into three sub-groups. The presence of a burrow is considered very specific (Level B1) but it is recognised that burrows are often not found even amongst cases of confirmed scabies [9]. Typical scabetic lesions on the male genitals are also considered very specific of scabies (Level B2). The final category of clinical scabies consists of those individuals with typical scabetic lesions (papules, vesicles) in the typical distribution of scabies accompanied by both itch in the patient and a close contact with either itch or a typical rash. Finally, ‘Suspected Scabies’ (Level C) is considered when either the clinical features or distribution of the rash are atypical or when only one of the two history features are present.

A first evaluation of a training package based around these criteria was undertaken in the Solomon Islands. The study was undertaken in school-aged children in a setting where the prevalence of both scabies and impetigo are extremely high [10, 11]. Nurses underwent a two-day training programme on the diagnosis of scabies based on the IACS criteria. The nurses undertook both a slide-based assessment reviewing clinical photos and accompanying details to make a presumptive diagnosis and a field-based assessment where their performance was assessed compared to a reference standard examination performed by a consultant paediatrician and a consultant dermatologist. Specificity was high for both the diagnosis of scabies (89.9%) and impetigo (97.7%) but the sensitivity was lower at only 55.3% and 52.6% respectively. There was evidence that the reduction in sensitivity was most marked amongst patients that the expert examiners classified as having 'mild' scabies, defined as 1–10 scabies lesions. Amongst individuals with moderate to severe scabies the sensitivity of the nurse led examination increased to 93.5% although this was accompanied by a reduction in specificity to 74% [10].

An additional consideration is the extent to which a limited examination may be suitable for scabies diagnosis under some circumstances. Full body examination is time-consuming, presents issues related to maintaining the privacy of the patient and is often not practical in resource limited settings. Diagnostic requirements may also vary when comparing the clinical setting where a decision is being made about individual patient management, as compared to diagnosis being made to inform a public health decision, such as whether or not to initiate MDA. In the latter scenario the decision is not made at an individual level and so a simplified examination may be acceptable if it still provides an accurate enough community level estimate of disease burden. Such approaches have been used in other Neglected Tropical Disease programmes [12]. The possibility of such an approach for scabies diagnosis within LMIC public health programmes has been explored in an initial retrospective study [13]. The authors combined data from a number of different scabies surveys conducted in the Pacific region. The body regions reported to have the highest diagnostic yield for scabies were he hands (51.2%), feet (49.7%), and lower legs (48.3%). Comparing examination of the exposed components of both limbs provided a sensitivity of 93.2% compared to full body examination. A limitation of this study is its retrospective nature and the possibility that all individuals may not have been fully examined, which could lead to an over-estimation of the sensitivity of a simplified examination. Prospective studies in both the Pacific and West Africa have also now suggested a simplified examination is likely to be accurate enough for public health implementation in resource poor-settings.

Whilst the IACS consensus criteria provide a clear step forward further work is needed to more precisely define the distribution and frequency of each type of scabies lesion. Studies in West Africa and the Pacific have demonstrated that the papule is the most frequent lesion type identified (found in >90% of cases) and that burrows, whilst classical for scabies, are found less commonly. Further work is also needed to standardise and validate training packages for scabies diagnosis in resource-poor settings and evaluate the performance of diagnostic algorithms in areas where other itchy skin conditions, such as onchocerciasis, are also common.

In summary and as in high-income settings, clinical examination of scabies is the mainstay of diagnosis in resource-poor settings. Diagnosis in this setting is reliant on mid-level health care workers. Training these individuals in the use of standardised criteria can achieve reasonable levels of sensitivity and specificity compared to a reference clinical examination. Scalable approaches to train mid-level healthcare workers in the use of a simplified examination and use of standardised diagnostic criteria are required to help drive forward scabies control at a global level.



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Potential for Sensitive and Simple Molecular Diagnostic Tools: Blood Tests for Scabies?

22

Romain Blaizot and Pascal Delaunay

22.1 Introduction: Scabies and the Need for New Diagnostic Methods

The diagnosis of scabies often relies on clinical examination. A clinical diagnosis is usually made in the presence of burrows or typical lesions affecting specific body areas, along with a history of familial itch [1]. However, typical lesions are not always present in ordinary scabies, which can be mistaken with many other cutaneous diseases, such as eczema, psoriasis, atopic dermatitis or irritant contact dermatitis [2]. The quality of the clinical diagnosis is directly linked to the clinician's experience. The evaluation of response to treatment is another issue, as active lesions due to persistent disease can be very hard to differentiate from secondary eczema or impetigo, or non-active residual lesions with no living mite. Sampling for diagnostic confirmation is not always performed, notably in the presence of specific clinical signs mentioned above, or when empirical treatment is started. Both of these situations do not require laboratory confirmation, which relies on viewing mites, their eggs or faeces. Hence, both of these situations rely on presumptive diagnosis.

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It is important to distinguish the different steps which lead to laboratory confirmation of human scabies, along with their respective sensitivity and specificity:

Dermoscopic examination may allow diagnosis of human scabies: In this case, definitive diagnosis requires observation of *Sarcoptes scabiei* mites or typical lesions, which can be hard to achieve. Moreover, dark skins may impede parasite identification. However, clinicians using dermatoscopes may examine multiple body parts in a short while, which increases diagnostic sensitivity. This explains why dermoscopic examination, when performed by experts, reaches up to 98% of sensitivity and specificity [1].

Microscopy requires previous scraping of an evocative lesion, which must contain elements that will prompt definitive diagnosis after slide mounting. Microscopic examination is not hampered by skin colour, contrarily to dermatoscopy. However, skin scraping is not always performed on every evocative lesion, given the subsequent discomfort for the patient. This particularity explains the lesser sensitivity for this technique, reaching 32% up to 38% when performed by experts [1]. Thus, microscopy requires specific skills which most general practitioners do not possess [3, 4]. It is mostly considered as Gold Standard but requires technical facilities which are mostly unavailable in remote areas or routine care in outpatient consultation.

Therefore, there is a need for new techniques offering improved sensitivity while requiring few technical skills. This is particularly important in ordinary scabies, the most common form of the disease, as crusted scabies is easier to diagnose [5]. Likewise, advanced scabies in animals is not difficult to identify due to the presence of many mites making microscopy easier and severe lesions [5]. Therefore, ordinary and mild presentations of scabies represent the main issue of improved diagnosis both in human and veterinary medicine.

22.2 PCR and Blood Tests Are Two Promising Pathways to Achieve This Objective

22.2.1 PCR

Given the limits described above for dermoscopic and microscopic diagnosis, the potential of a PCR tool for the diagnosis of human scabies is obvious. A well-designed PCR diagnostic assay should be 100% specific for *Sarcoptes scabiei*. The presence of mites, eggs or even fragments obtained through sampling may allow very high sensitivity for the PCR assay (near 100%). As scabies is a disease of the upper layers of the skin, parasites are retrievable by samplings with swabs, biopsies or scrapings for detection of adults larvae, eggs or dejections. The sampling step is therefore crucial for PCR diagnosis; indeed, sampling must collect as much pathological material as possible. However, proper skin sampling should not be too operator-dependent for the clinician, and should be as painless as possible for the patient.

22.2.2 Historical Perspective

The first published experiment of PCR as a diagnostic tool for scabies was conducted in Germany in 2001 on 44 DNA samples obtained from skin scales or skin biopsies (fresh or extracted from formalin-fixed tissues) [2]. PCR yielded a disappointing sensitivity but its performances were improved by using an ELISA technique on the PCR products. However, these results are to be taken with caution as the Gold Standard in this study was histology. The poor quality of DNA extraction from formalin-fixed tissues is also a factor of decreased performances. A Japanese study in 2010 reported inferior sensitivity of PCR when compared to clinical examination, suggesting that the compared performance of PCR could be even lower with microscopy [3].

These earlier studies were then followed by much more promising experiments. In 2015 in Italy, Angelone-Alasaad et al. included samples from 14 countries, mostly from animal hosts, and reported 100% sensitivity and positivity, compared with microscopy [4]. However, this experimental and mostly veterinarian study did not mirror routine conditions of clinical care of scabies. PCR was once again found to be superior to microscopy in a new study in Hong Kong in 2015, with sensitivities of 100% and 58.7%, respectively [5]. These promising performances were further enhanced by two Korean studies. The first one [6] improved the sensitivity reported by Wong et al. by using a nested PCR. Sequencing and BLAST analyses were used to provide a precise species diagnosis which would not be hampered by the presence of dust mites genetically closed to *S. scabiei*. The second study [7] provided interesting results regarding the IACS (International Alliance for the Control of Scabies) diagnostic criteria [8]. Indeed, though the overall performances of PCR remained good, its sensitivity was superior to that of microscopy only when including confirmed, clinical and suspect scabies. On the other hand, when restricting the analyses to patients with confirmed or confirmed and clinical scabies, the sensitivity of PCR was inferior to microscopy.

A summary of these studies is presented in Table 22.1.

The most recent study was conducted in Korea [7]. PCR allowed the detection of five additional cases, compared with microscopy, highlighting the potential for this technique in increasing sensitivity. The performances of both microscopic examination and PCR decreased proportionally with the level of diagnostic certainty. The most likely explanation, as pointed out by the authors, was that some patients with clinical or suspect scabies did not actually have scabies. It is noteworthy that while the sensitivity of both tests decreased, that of PCR decreased less than that of microscopic examination. The sensitivity of PCR was indeed higher than microscopic examination when including confirmed, clinical and suspected scabies (80% vs. 73%). However, it remained lower than that of microscopy in confirmed scabies (86% vs. 100%) or when including only confirmed and clinical scabies (83% vs. 92%). In the control group formed with patients with other skin diseases, the specificity of the scabies PCR was 100%. Therefore, this PCR seemed particularly useful in case of suspected scabies without the full IACS criteria.

Table 22.1 Review of PCR scabies studies

Reference	Year	Country	Size	Compared to	Target gene	PCR method	Sampling	Results
Bezold et al.	2001	Germany	44 DNA samples	Histology	Sarms15 and ß-globin	PCR + ELISA	Skin scales samples, fresh and formalin-fixed skin biopsies	Low sensitivity with PCR only, improved with ELISA
Fukuyama et al.	2010	Japan	91	Clinical examination	SMH and ITS-2	Nested PCR + BLAST	Scrapings	43.1% and 56.8% in confirmed scabies; 37.5% and 57.5% in suspected scabies in SMH and ITS-2 respectively: ITS-2 more sensitive than SMH
Angelone-Alasaad	2015	Italy (samples from 14 countries)	48 (3 humans and diverse animals)	Microscopy	16S rDNA with specific universal primers designed from sequencing of first products	Conventional end-point PCR; real-time Taqman PCR	Scrapings	100% positivity and sensitivity; lower threshold in real-time PCR compared with conventional (10 pg/µL vs. 80)
Wong et al.	2015	Hong Kong	100	Microscopy	Cox-1	Conventional and real-time qPCR	Scrapings (+swabs if crusted scabies)	PCR positive in all microscopy-positive patients and 14% of microscopy-negative patients; PCR sensitivity 100% > microscopy 58.7%

Hahm et al.	2018	Korea	61	Dermatoscopy + microscopy	Cox 1, ß-globin, EF-1α	Nested PCR + BLAST	Scrapings	PCR sensitivity 100% > DSGSS-ME (75.68%) with 100% positive PCR in microscopy-positive and 26% of microscopy-negative patients; nested PCR > conventional in Wong et al.
Delaunay et al.	2020	France	164	Dermatoscopy + clinical examination by expert	ITS-2	Standard PCR + BLAST	Swabs	PCR sensitivity 37.9% in confirmed scabies; 20.1% in suspected scabies; 99.1% after 10 samplings, useful in outbreak investigation PPV 100%
Bae et al.	2020	Korea	47	Microscopy, clinical examination (IACS criteria)	Cox 1	Real-time PCR + BLAST	Scrapings	PCR specificity 100%; sensitivity > microscopy in confirmed/clinical/ suspected scabies (80% vs. 73%); lower in confirmed or confirmed/ clinical scabies (86% vs. 100%; 83% vs. 92%)

22.2.3 Outbreak Investigation

Outbreak investigations represent a specific setting when a quick diagnosis is required to avoid public health consequences. These outbreaks are likely to break to occur in non-medicalised settings such as elderly care homes. Therefore, diagnostic methods such as dermatoscopy or microscopy, which require specific skills, are mostly unavailable. A recent French study provided hints for the possibility of diagnosing large outbreaks with repeated dry swabs samplings [1]. Sensitivity was close to microscopy with 37.9% in confirmed scabies and 20.1% in suspect scabies. However, positive predictive value (PPV) was 100%. Due to this PPV, the authors pointed out the utility of this method in suspicion of outbreaks, by allowing the quick and easy identification of at least one case, allowing the extrapolation of this positive result to other symptomatic patients of the outbreak. The authors standardised sampling on all eight interdigital spaces and both wrists and any other lesion to improve the sensitivity. The low performances of PCR would be balanced by the sampling of many patients in an outbreak, as taking samples from several people increased the likeliness of yielding at least one positive result. Indeed, sensitivity in the cluster was as high as 99.1% after 10 samplings.

22.2.4 Method of PCR

Concerning the method of PCR, nested PCR certainly improves the detection threshold, when compared to standard PCR, as demonstrated in Hahm et al. [6]. The authors showed an improved sensitivity with nested PCR compared to conventional method. Their initial hypothesis was that the absence of dermatoscopy to guide microscopy in previous reports undermined the sensitivity of microscopy. However, even with DSGSS-ME, microscopy remained less sensitive (75.68%) than PCR (100%). PCR was always positive in microscopy positive patients, while 26% of microscopy negative patients were positive in PCR. In Angelone et al., real-time Taqman PCR was more sensitive than conventional end-point PCR, with a lower threshold (80 vs. 10 pg/µl) [4]. However, both techniques had 100% positivity and sensitivity in scrapings for 48 samples from many different hosts (including only 3 human samples). Twenty-three host species from 14 countries were included in this study which proposed a useful and very sensitive method to be used both in human and veterinary medicine.

22.2.5 PCR Targets

Concerning targets, *cox 1* gene is used in most aforementioned studies. Numerous sequences of this gene are available. It is important to avoid false positive results due to cross reaction with other pathogens such as dust mites [1]. Using specific targets and sequencing analysis with BLAST are useful ways to reduce this bias. Moreover, this mitochondrial gene has no high level of similarity with zoonotic

mites, dust mites or other human skin mites [5]. A study in Japan in 2010 [3] reported better performances with ITS-2 as a target. Sensitivity remained low with around 57% in confirmed or suspected scabies.

22.2.6 Sampling Method

Concerning the sampling method, most studies have used either scrapings or biopsies. Delaunay et al. recently showed how swabs could yield similar results than scrapings [1]. Swabs, however, are much easier to perform and can be repeated to increase sensitivity. Adhesive tape test is another method of collecting mites which has been evaluated against dermatoscopy and scrapings in Brazil, with good positive and predictive values [9]. However, adhesive tape was then used for microscopy and not for PCR. Adhesive tapes are easier and quicker to perform than scrapings, and such techniques have already been evaluated for PCR with other parasitic diseases such as cutaneous leishmaniasis [10]. Further studies are needed to explore this sampling method, notably quantitative PCR to assess the parasite load retrieved with swabs, scrapings or tape tests.

The combination of PCR and ELISA was evaluated in a small study in Germany [2]. Agarose-gel analysis was not sensitive enough and had to be improved with ELISA, allowing a very good specificity. The genetic diversity of mites infecting a same human host does not make the interpretation of agarose-gel analysis easier. Cutaneous scales were more positive than biopsies, which was expected given that scabies live in the upper layer of the epidermis.

22.2.7 Obstacles: Genetic Diversity, Interaction with House Dust Mites, and Cost

The genetic diversity of *S. scabiei* could be an obstacle to a good sensitivity of PCR, as different clades might be encountered in sarcoptic infections, some of which might not be detected by the designed probe [7]. Contrary to the initial hypothesis that *S. scabiei* was divided into different varieties according to hosts, a recent study identified three clades of *S. scabiei* in mites collected among humans and animals, irrespective of host species. This study was based on PCR and sequencing of *cox 1* gene and showed a very high genetic diversity of this gene [11].

PCR is usually seen as a costly diagnostic method and its use in a neglected tropical disease such as scabies could seem irrelevant. However, one of the very interesting points discussed in Wong et al. [5] was cost-efficiency. Each test of conventional and qPCR was estimated to cost approximately $6.7 and $11.0, while the cost of microscopy was $3.9. This cost was estimated at 3.2£ in a German study [2]. As PCR should allow identification of infested patients at an earlier stage and minimise the size of outbreaks, its use could eventually prove cost-efficient in developed countries by reducing the cost of work interruption and service disruption. This point should also be discussed in low-resources settings of tropical areas. The lack

of medical staff or other health workers with specific skills makes PCR very promising for remote endemic areas. Gathering samples from many isolated villages and performing PCR in a referral urban centre could be a way to maximise cost-efficiency while ensuring a prompt and easy in under-medicalised populations. The development of other PCR formats known for their simplicity, such as loop-mediated isothermal amplification (LAMP) could further reduce the cost of PCR for low-resources settings [5]. Quantitate methods present additional costs which are not required for routine clinical care and should be reserved to research purposes [5].

22.3 Blood Tests

The development of new techniques of PCR and blood tests are closely entwined. Indeed, the expansion of our knowledge of scabies genomics allows the identification of new proteins and antigens linked to host infestation and response. These findings in turn allow the creation of new tools for diagnosing scabies active infection in human blood [12]. For example, it is known that the genome of *S. scabiei* var. *canis* contains a large proportion of homologs in the genome of the 33 dust mites allergens [13]. Identifying heterologs in *S. scabiei* which are not represented in dust mites is key to the creation of specific blood markers, as cross-reactivity with dust mites antigens is the most likely source of false positive results [14].

Genomics also allow the identification of proteins deeply involved in the infestation process, such as the immunomodulation of host defences, which are more most likely to be highly expressed in the early stages of infection, and would therefore be of great use in clinical routine. However, some of these genes are also expressed in other parasite and blood-sucking arthropods such as ticks, as their infestation process in the upper layers of the skin is similar to that of scabies [12]. Besides, some proteins might be involved in the infestation process but would not bind circulating antibodies, as they are only involved at a local cutaneous level [15]. These findings underline the different qualities required for a good blood test target: relevance in the setting of clinical infestation, circulation in human blood and specificity for *S. scabiei.*

Though scabies is easy to diagnose in case of crusted scabies, classic scabies can be challenging, particularly for a non-experienced physician. The number of adult mites in a, infected human presenting ordinary scabies is estimated at 15 [12]. Therefore, microscopy is also likely to be falsely positive. For many years, researchers have tried and still try to create a blood test which would be easy to perform, allowing a quick diagnosis even for non-experienced doctors or nurses, while retaining a good specificity. However, these studies have met a number of obstacles.

22.3.1 Obstacles: Genetic Diversity, Interaction with Dust Mites, Kinetics and Clinical Relevance

As in PCR, the genetic diversity of *S. scabiei* represents a major obstacle. Different strains can be involved according to the geographical area involved and different strains might even be involved in a same infected human [16]. This makes the use

of a cocktail of antigens most likely to allow a fairly sensitive blood test [17]. Specific tests could also be designed for different continents or areas. Exhaustive data on the genetic diversity of *S. scabiei* in isolated areas and neglected populations is important to ensure future tests would be adapted to these fragile groups.

It is admitted that there exists only one species of *S. scabiei* with three different strains and a high intra-species variability. The genomes of the three main strains of *Sarcoptes scabiei* var. *canis*, *hominis* and *suis* are very close to each other. Genomic data are available for these three strains in public databases [13, 18, 19]. However, extrapolation between studies on different hosts is an important matter, as many studies are conducted on *var. canis* or *var. suis* and might find results which would not be identical in humans. For example, when comparing the performances of an ELISA test in var. vulpes, different sensitivities were found among hosts, lower in humans [20] than in pigs [21] or dogs [22].

In the first studies on blood tests for scabies, it was demonstrated that IgA levels were higher 6 weeks after infection that at baseline [23]. However, these results did not suggest practical use for routine care, as what clinicians need is an answer at baseline. Likewise, scabies has been shown to increase IgE production [23]. When studying the utility of recombinant ELISA in pigs mange, Casais et al. noticed that pigs developed IgG between 4 and 8 weeks after infection and kept these antibodies for months [24]. Therefore, high IgG titre would not allow the distinction between acute infection and past contact. However, different antigenic fractions are recognised during acute and chronic infections [25]. The authors also raised the possibility that asymptomatic viral infections in pigs could hamper the immune reaction to scabies and decrease the creation of antibodies. Van der Heijden et al. showed that both ELISA and Sarcoptes became positive several weeks after the first symptoms. The study was conducted among pigs but similar results are likely to be obtained in humans [26].

Among the different types of antibodies produced during host response, IgM are the most interesting, as they are developed at the early stage of infection and would therefore be most useful for initial diagnosis. IgG would appear too late to allow an initial diagnosis of scabies and could remain positive after the infection is cured. Though the production of IgE has been evaluated in many studies, their use in a routine diagnosis of scabies at an early stage of infection and in the general population is unlikely. Though IgE are often produced by hosts infected with crusted scabies, they are often lacking in ordinary scabies [27].

22.3.2 Recombinant ELISA: A Promising Pathway

One of the serious issues encountered in the conception of serological diagnosis of scabies is the difficulty to cultivate mites to yield enough material. Therefore, the use of recombinant proteins has been proposed as an effective way to produce antigens from Escherichia coli cultures [28]. An ELISA based on one of these recombinant antigens was evaluated in a comparative study of two panels of infested and healthy rabbits in 2015, with a 95% to 100% sensitivity and a 90% to 97% specificity [29]. However, the authors also tested the ELISA on rabbits infected with

psoroptic mange and found positive results in 42% of them, indicating a possible cross-reaction with different mites species. Seroconversion in positive rabbits occurred mostly after 2 weeks of infection, highlighting a possible use in clinical practice [29]. However, these promising studies need to be performed in humans before any routine use can be contemplated.

22.4 Conclusion

Several improvements are needed to allow the use of scabies PCR in routine clinical care. However, repeated swab samplings are probably the best way to collect enough DNA material on human skin. PCR can then be of help in patients with suspected scabies without clinical or confirmed IACS criteria. Outbreak investigation is another noteworthy indication. Larger studies involving non-invasive samplings should be able to increase overall sensitivity by improving the collection of sarcoptic fragments. Concerning blood tests, they are still far from representing a routine option. However, a serologic test for scabies would be an even easier diagnostic tool than PCR. Therefore, this field of research deserves further studies.

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Sarcoptic Mange in Wild and Domestic Animals

23

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23.1 Introduction

The presence of *Sarcoptes scabiei* was reported in a wide range of mammalian species, including humans, domestic and wild animals. Scabies is the name of the skin disease caused by *S. scabiei* in humans whereas in animals the disease is usually referred to as sarcoptic mange. Other mites (*Psoroptes*, *Chorioptes*, *Otodectes* or *Notoedres* spp.) are also responsible for mange in animals. All these diseases are highly contagious in animal populations and are associated with hair loss, crusts and

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pruritus. In humans, scabies has been known from ancient times the first mention being in the Bible. In animals, the first reports on mange appear to be in sheep, also in the Bible, where in the Leviticus it was written that sheep suffering from mange (most probably psoroptic mange) could not be offered as sacrifice. The interest in mange in sheep continued during Roman times, with recommendation of treatment written by several authors, Virgil describing in his poetic agricultural manual Georgics, the problems caused by mange and its treatment by tar, grease and washing in sheep [1]. In 1786, a German physician, Johann Ernst Wichmann published a monograph which provided detailed drawings of the mites and stated that mange in sheep, like in humans, is due to mites. In 1812, veterinarians from the veterinary college of Lyon, France collected and described *S. scabiei* mites from lesions in horses and cattle. It has been proposed that humans and earlier protohumans were the source of *Sarcoptes* mites, first for dogs, and later for other species with subsequent spread to wild mammals [2, 3]. Variant forms of *S. scabiei* are named based on the host species from which they are isolated (e.g., *S. scabiei* var. *suis* from pigs, *S. scabiei* var. *cuniculi* from rabbits) and inability to cause severe and permanent clinical infection in distinct animal hosts [3, 4]. In animals, sarcoptic mange is usually characterized by the succession of different phases namely an incubation period (2–3 weeks after exposure to the mites), a hyperergic phase lasting for several weeks or months and a desensitization period leading to a total or partial elimination of *Sarcoptes* mites from the skin.

23.2 Sarcoptic Mange in Wildlife

23.2.1 A Major Concern for Several Mammalian Species

To date, the infection by *S. scabiei* has been reported from 10 orders, 33 families and 148 mammalian species (Table 23.1). Most of these species are represented by free-ranging or wild mammals worldwide [63]. In Europe, sarcoptic mange is recognized as a common cause of mortality in chamois [87, 101], Spanish ibex [154, 156] and red foxes [49, 50, 157]. The disease was reported also in several other ruminants and carnivores [23, 28, 59]. In Asia, ruminants are the most prominent wildlife species with sarcoptic mange [7]. In Africa, the list of infected species includes apes (gorillas and chimpanzees), lions, cheetahs, giraffes and several other herbivores [10, 36, 102, 115, 116]. In Australia, wombats, wallabies and dingoes are frequently affected [148, 153, 155, 158]). In North America, canids (foxes, coyotes, wolves and American black bears) are the main hosts whereas sarcoptic mange seems to be much less frequent in bovids than in other continents [25, 77, 159]. A few reports indicate that wild carnivores are infected in South America [41, 57] and sarcoptic mange is commonly found in captive small camelids (llamas and alpagas) originating from South America but living in other continents. The disease was suggested also as a major concern in the native rodent capybara [126].

In wildlife, sarcoptic mange is usually characterized by an initial epizootic phase followed by an enzootic cycle with lower prevalence and potential fade-out. Major outbreaks were described and analyzed in red foxes in Europe [157], wolves and black bears in North America [159], kit foxes in California [43], ibex in Spain [156,

Table 23.1 List of mammals with reported *Sarcoptes scabiei* infection

Classification	Species	Scientific name	Locality	Selected references
EUTHERIA/Order Primates (about 375 species in 15 Families)				
Atelidae	Black spider monkey	*Ateles paniscus*	Brasil	[5]
Callitrichidae	Common marmoset	*Callithrix jacchus*	Brasil	[5]
Cercopithecidae	Long-tailed macaque	*Macaca fascicularis*	Denmark[a]	[6]
	Rhesus monkey	*Macaca mulata*	China	[7]
	Bonnet monkey	*Macaca radiata*	India[a]	[8]
Hominidae	Man	*Homo sapiens*	Global	[9]
	Gorilla	*Gorilla beringei beringei*	Uganda	[10, 11]
Pongidae	Chimpanzee	*Pan troglodytes*	Africa	[12]
	Pygmy chimpanzee	*Pan paniscus*	Africa	[12]
	Orangutang	*Pongo pygmaeus*	The Netherlands[a]	[3]
	Gibbon	*Hylobates leuciscos*	USA[a]	[3]
EUTHERIA/Order Carnivora (about 290 species in 15 Families)				
Ailuridae	Red panda	*Ailurus fulgens*	China	[7]
Canidae	Arctic fox	*Alopex lagopus*	Europe	[13]
	Dog[b]	*Canis familiaris*	Global[a]	[14– 17]
	Dingo	*Canis familiaris dingo*	Australia	[18, 19]
	Coyote	*Canis latrans*	America	[20–22]
	Grey wolf	*Canis lupus*	North America, Scandinavia, Iberian peninsula	[21–29]
	Golden jackal	*Canis aureus*	Israel	[30]
	Jackal	*Canis mesomelas*	Africa, India	[12, 31]
	Red wolf	*Canis rufus*	North America	[32]
	Crab-eating fox	*Cerdocyon thous*	South America	[3, 33]

(continued)

Table 23.1 (continued)

Classification	Species	Scientific name	Locality	Selected references
	Maned wolf	*Chrysocyon brachyurus*	Bolivia	[34]
	Chilla fox	*Lycalopex griséus*	Chile	[35]
	Wild dog	*Lycaon pictus*	Africa	[36, 37]
	Raccoon dog	*Nyctereutes procyonoides*	Europe, Japan, Korea[a]	[28, 38–40]
	Pampas fox	*Pseudalopex gymnocercus*	Bolivia	[41]
	Gray fox	*Urocyon cinereoargenteus*	North America	[42]
	Kit fox	*Vulpes macrotis mútica*	California	[43]
	Red fox	*Vulpes vulpes*	Europe, North America, Australia	[18, 28, 44–50]
Felidae	Cheetah	*Acinonyx jubatus*	Africa	[36, 51]
	Chinese mountain cat	*Felis bieti*	China	[7]
	Cat[b]	*Felis catus*	Global	[52–55]
	Cougar	*Felis concolor*	USA[a]	[56]
	Serval	*Felis serval*	Africa	[12]
	Margay	*Leopardus wiedii*	South America	[57]
	Lynx	*Lynx lynx*	China[a], Europe, Pakistan	[23, 58–60]
	Iberian lynx	*Lynx pardinus*	Spain	[61]
	Lion	*Panthera leo*	Africa	[51, 62]
	Jaguar	*Panthera onca*	USA[a]	[56]
	Leopard	*Panthera pardus*	Germany[a], USA[a], South Africa	[56, 63]
	Tiger	*Panthera tigris*	Vietnam[a]	[64]
	Snow leopard	*Uncia uncia*	The Netherlands[a]	[65]

Mustelidae	Stone marten	*Martes foina*	Europe	[28, 66]
	Pine marten	*Martes martes*	Europe	[23, 66]
	Japanese Marten	*Martes melampus*	Japan	[67]
	Fisher	*Martes pennanti*	North America	[68]
	Japanese badger	*Meles anakuma*	Japan	[67]
	Badger	*Meles meles*	Europe	[28]
	Siberian polecat	*Mustela putorius*	Europe	[69]
	Ferret[b]	*Mustela putorius furo*	Global	[70]
Phocidae	Harbor seal	*Phoca vitulina*	Europe	[71]
Procyonidae	Feral Raccoon	*Procyon lotor*	Japan, USA, Germany	[67, 72, 73]
	South American coati	*Nasua nasua*	England[a]	[3]
Protelidae	Aardwolf	*Proteles cirstatus*	Africa	[12]
Ursidae	Polar bear	*Thalarctos maritimus*	Czech Republic[a]	[74]
	Black bear	*Ursus americanus*	North America	[75–77]
	Brown bear	*Ursus arctos*	Czech Republic[a]	[74]
EUTHERIA/Order Artiodactyla (about 240 species in 10 Families)				
Bovidae	Impala	*Aepyceros melampus*	Africa	[12]
	Hartebeest	*Alcelaphus buselaphus*	Africa	[12]
	Barbary sheep[b]	*Ammontragus lervia*	Israel	[78]
	Springbok	*Antidorcas marsupialis*	Africa	[12]
	Pronghorn	*Antilope cervicapra*	Czech Republic[a]	[79]
	Zebu[b]	*Bos taurus indicus*	Africa	[37, 51][a]
	Cattle[b]	*Bos taurus*	Global[a]	[3, 80]
	Nilgai	*Boselaphus tragocamelus*	USA	[81]
	Water buffalo[b]	*Bubalus bubalis*	Asia	[82–84]
	Goat[b]	*Capra hircus*	Global	[3, 37, 85, 86]
	Alpine Ibex	*Capra ibex*	Europe	[87, 88]

(continued)

Table 23.1 (continued)

Classification	Species	Scientific name	Locality	Selected references
	Nubian ibex	*Capra nubiana*	Israel[a]	[78]
	Iberian ibex	*Capra pyrenaica*	Europe	[89]
	Siberian ibex	*Capra sibirica*	Asia	[90]
	Japanese serow	*Capricornis crispus*	Japan	[67]
	Formosan serow	*Capricornis swinhoei*	Taiwan	[91]
	Himalayan serow	*Capricornis thar*	India	[92]
	Common wildebeeste	*Connochaetes taurinus*	Africa	[12, 37]
	Mountain gazelle	*Gazella gazella*	Israel[a]	[78]
	Grants gazelle	*Gazella granti*	Africa	[93]
	Goitered gazelle	*Gazella subgutturosa*	Iran	[94]
	Thomson's gazelle	*Gazellea thomsoni*	Africa	[95, 51]
	Sable antelope	*Hippotragus niger*	Africa	[62]
	Waterbuck	*Kobus ellipsiprymnus*	Czech Republic[a]	[79]
	Goral	*Naemorhedus goral*	Asia	[7]
	Arabian oryx	*Oryx leucoryx*	Israel[a]	[78]
	Sheep[b]	*Ovis aries*	Global	[3, 37, 80, 96, 97]
	European Mouflon	*Ovis qries musimon*	Europe	[98]
	Urial	*Ovis vignei*	Pakistan	[99]
	Blue Sheep	*Pseudois nayaur*	Pakistan	[100]
	Steenbok	*Raphicerus campestris*	Africa	[12]
	Southern chamois	*Rupicapra pyrenaica*	Spain	[101]
	Northern chamois	*Rupicapra rupicapra*	Europe	[87]
	African buffalo	*Syncerus caffer*	Africa	[12, 102]
	Eland antelope	*Taurotragus oryx*	Israel[a]	[78]
	Greater kudu	*Tragelaphus strepsiceros*	Africa	[12]

Camelidae	Bactrian camel[b]	*Camelus bactrianus*	UK	[3]
	Dromedary[b]	*Camelus dromedarius*	Asia[a], Arabia[a], Africa[a]	[103–106]
	Llama[b]	*Lama glama*	– Portugal	[98, 107]
	Guanaco	*Lama guanicoe*	–	[98]
	Alpaca[b]	*Vicugna pacos*	Europe, New Zealand	[98, 108, 109]
	Vicuna	*Vicugna vicugna*	–	[98]
Cervidae	Moose	*Alces alces*	Germany[a]	[110]
	Roe deer	*Capreolus capreolus*	–	[98, 111, 112][a]
	Fallow deer	*Cervus dama*	Spain	[113]
	Red deer	*Cervus elaphus*	Europe	[98, 112]
	Sika deer	*Cervus nippon*	China	[7]
	Sambar	*Cervus unicolor*	Asia	[3]
	Tufted deer	*Elaphodus cephalophus*	Asia	[7]
	White-tailed deer	*Odocoileus virginianus*	USA	[81]
	Reindeer	*Rangifer tarandus*	Russia[a]	[114]
Giraffidae	Giraffe	*Giraffa camelopardalis*	France[a], Kenya	[115–117],
	Warthog	*Phacochoerus aethiopicus*	Africa	[3]
	Wild boar or pig[b]	*Sus scrofa*	Europe, North Amer. Global	[3, 69, 118–121]
	Japanese wild boar	*Sus scrofa leucomystax*	Japan	[67]
Tayassuidae	White-lipped peccary	*Tayassu pecari*	America	[3]
	Collared peccary	*Tayassu tajacu*	USA[a]	[122]
EUTHERIA/Order Hyrachoidea (4 species in 1 Family)				
Procaviidae	Daman	*Heterohyrax syriacus*	Africa	[93]
	Rock hyrax	*Procavia capensis*	Africa	[93]

(continued)

Table 23.1 (continued)

Classification	Species	Scientific name	Locality	Selected references
EUTHERIA/Order Perissodactyla (17 species in 3 Families)				
Equidae	Donkey[b]	*Equus asinus*	Arabia, UK	[123, 124]
	Horse[b]	*Equus caballus*	Global	[3, 80, 123]
Tapiridae	Tapir	*Tapirus terrestres*	Europe[a], USA[a]	[3, 79, 125]
EUTHERIA/Order Rodentia (about 2,300 species in 30 Families)				
Caviidae	Guinea pig[b]	*Cavia porcellus*	France	[3]
	Capybara	*Hydrochoerus hydrochaeris*	Europe[a], South America	[3, 126]
Erethizontidae	Andean porcupine	*Coendou quichua*	Colombia	[127]
	North American porcupine	*Erethizon dorsatum*	North America	[128]
	Crested porcupine	*Hystrix cristata*	Italy	[129]
Muridae	African giant pouched rat	*Cricetomys gambianus*	Africa	[3]
	House mouse	*Mus musculus*	USA[a]	[122]
Sciuridae	Fox squirrel	*Sciurus niger*	North America	[130]
EUTHERIA/Order Lagomorpha (92 species in 3 Families)				
Leporidae	Brown hare	*Lepus europaeus*	Europe	[131]
	Mountain hare	*Lepus timidus*	Europe	[132]
	Rabbit[b]	*Oryctolagus cuniculus*	Global	[3, 133, 134]
	Swamp rabbit	*Sylvilagus aquaticus*	USA	[135]
	Marsh rabbit	*Sylvilagus palustris*	USA	[135]
EUTHERIA/Order Erinaceomorpha (24 species in 1 Family)				

Erinaceidae	African hedgehog	*Atelerix albiventris*	Africa	[136]
	North african hedgehog	*Atelerix algirus*	North Africa	[137]
	Southern white-breasted hedgehog	*Erinaceus concolor*	Israel	[138]
	European hedgehog	*Erinaceus europaeus*	Israel, Germany, New Zealand	[139–141]
	Long-eared hedgehog	*Hemiechinus auritus*	Israel[a]	[78]
EUTHERIA/Order Pilosa (10 species in 4 Families)				
Bradypodidae	Brown-throated sloth	*Bradypus variegatus*	Brasil[a]	[142]
METATHERIA (Marsupials)/Order Diprotodontia (about 140 species in 11 Families)				
Macropodidae	Agile wallaby	*Macropus agilis*	Australia	[143]
	Swamp wallaby	*Wallabia bicolor*	Australia	[144]
Peramelidae	Southern Brown bandicoot	*Isoodon obesulus*	Australia	[145]
Phascolarctidae	Koala	*Phascolarctos cinereus*	Australia	[146, 147]
Pseudocheiridae	Common ringtail possum	*Pseudocheirus peregrinus*	Australia	[148]
Vombatidae	Southern hairy-nosed wombat	*Lasiorhinus latifrons*	Australia	[3, 149–151]
	Common wombat	*Vombatus ursinus*	Australia	[18, 152, 153]

[a]Wild animals in captivity
[B]Domestic animals
– not indicated

160], chamoix in Italy [87], raccoons in Asia [39, 40] and bare-nosed wombats in Australia [148]. The source of these outbreaks is usually unknown, with potential transmission from domestic animals (cattle, sheep or dogs) or from infected preys in the case of carnivores. Infected animals typically suffer from dramatic structural and functional changes in the skin, becoming listless, dehydrated, emaciated and eventually dying [63] (Fig. 23.1). Martin et al. [161] investigated the pathogenic

Fig. 23.1 Lesions of sarcoptic mange in wild animals. (**a**) A young wild boar (*Sus scrofa*) in Italy (courtesy of Luca Rossi), (**b**) A roe dear (*Capreolus capreolus*) in Italy (courtesy of Luca Rossi), (**c**) A European mouflon (*Ovis aries musimon*) in Italy (courtesy of Luca Rossi), (**d**) A red fox (*Vulpes vulpes*) in France (courtesy of Parasitology dept, EnvA), (**e**) A common wombat (*Vombatus ursinus*) in Australia (courtesy of Richard Malik), (**f**) The same animal after treatment (courtesy of Richard Malik)

impacts of mange in bare-nosed wombats. Using thermal imaging, they clearly demonstrated that infected wombats lose more heat to the environment from alopecia-affected body sites than healthy animals. Furthermore, infected wombats had higher metabolic rates whereas they spent less time foraging and more time inactive relative to healthy counterparts. Lastly, *Sarcoptes* infection was associated with an altered fatty acid composition in adipose tissue.

In wild animals, mite transmission occurs through both direct contact in social species as well as indirect transmission in more solitary species. Shared dens likely represent the most dominant mechanism of mite transmission among wombats in Australia [162] or kit foxes in North America [163]. Dens may also be a major source of contamination within and between carnivore species in Europe [28].

23.2.2 Surveillance of Infection and Mite Exposure in Wild Animal Populations

Despite difficulties which are intrinsic to research on wildlife models, various methods for the field monitoring of sarcoptic mange in free-ranging mammals have been developed. Visual diagnosis from distance is still in large use. However, both false negatives (particularly in the early stages of the disease) and false positives (because of confounding conditions such as molting) may arise. The sensitivity and specificity of visual diagnosis have been recently established in Iberian ibex (*Capra pyrenaica*), showing that both parameters are remarkably affected by factors such as age, sex and season [164]. Due to these limitations, other complementary or alternative noninvasive methods have been explored, including camera-trapping, use of trained dogs and thermography. The first of these methods, in large use for wildlife documentation and research purposes worldwide, has proved particularly useful to investigate the apparent prevalence and spatiotemporal dynamics of sarcoptic mange in elusive wild carnivores [27, 49, 81, 165, 166], and ungulates [81, 167]. Trained detector dogs were very effective in localizing dead or moribund sick chamois in the Alps [115, 116], thus increasing the sample size in a mortality study of epidemic mange [168]. Infrared thermography, through which heat loss from bare skin lesions may be visualized from distance, is another promising noninvasive method for mange surveillance and pathophysiological studies of the disease [169]. Increasingly performant devices entering the market will likely improve the detection of small-sized lesions in the range of several hundred meters from the target [170]. Standardized longitudinal interviews of skilled game wardens were also used, in parallel with other tools (including camera trapping and the screening of a large database of necropsy reports from general health surveillance and sylvatic rabies surveillance), in a study of the long-term dynamics of sarcoptic mange in the red fox [49]. The combination of multiple surveillance tools undoubtedly proved to be a successful strategy to cope with the study objectives.

Other methods in use for field studies of mange in wildlife imply live capture and handling of *Sarcoptes* exposed individuals. Fitting Iberian ibex with GPS

radio-collars was fundamental to demonstrate the spontaneous resolution of mange in a high percentage of individuals within an enzootically infected population and calculate the average recovery time of resistant animals, together with the survival time of nonresistant ones [171]. Studies in VHF radio-collared carnivores resulted in fine-tuning of mange prevalence and mortality parameters estimates, and yielded valuable data on the space use and life expectancy of affected individuals compared with healthy ones [157, 172–174].

Serodiagnosis and serosurveillance of *Sarcoptes* infection (by various in-house or commercially available ELISA tests) have been also been applied to experimental and spontaneous wildlife models including ruminants [175–177], carnivores [29, 48], pigs [178] and lagomorphs [134, 179]. Of note, the availability of serological methods opened the doors for retrospective epidemiological studies of stored samples and facilitated the study of sarcoptic mange in elusive hosts and/or partially resistant and only mildly symptomatic host populations [178]. Finally, molecular tools are increasingly being used for a better understanding of the epidemiology of sarcoptic mange in wildlife and at the livestock/wildlife interface, and address theoretical and practical questions on the origin and cross-transmissibility of *S. scabiei* within natural or human-manipulated multihost systems.

Data generated by studies taking advantage of the aforementioned tools will expectedly feed epidemiological modeling approaches, to explore in particular the relationships between mange outbreaks and host demography, with the ultimate goal to address the relevant conservation strategies when applicable. In turn, development of the models will highlight "gray" knowledge areas in need of prioritization, as shown by available modeling studies of epizootic mange in chamois [180, 181].

23.2.3 Control Strategies of Sarcoptic Mange in Wildlife

How to manage sanitary emergencies in free-ranging wildlife is known to be an unfading matter of debate, in which technical and professional aspects inevitably mingle with ethical issues and the vision of the planet, its inhabitants and their equilibria [182]. Sarcoptic mange outbreaks are no exception, and there is limited evidence-based scientific literature on the efficacy and sustainability of control strategies in wildlife. In general, major outbreaks affecting large-sized populations (e.g., several mountain-dwelling Caprinae in Europe and Asia) have been allowed to run their course undisturbed ("*laissez-faire* strategy," according to [182]), with the exception of humane suppression of severely sick individuals to meet emotional ("ethic") expectations. Apparently, no or just minor long-term effects on host abundance have been documented, at least in carnivores [63].

However, proactive control strategies have been implemented by the relevant wildlife management agencies in the case of: (1) valuable game species, to limit the impact on the economy of rural communities largely depending on hunting revenues; (2) vulnerable species or small-sized populations, for conservation purposes; (3) iconic and tame species (e.g., the common wombat, *Vombatus ursinus*). Meneguz

et al. [183] and two recent reviews by Perez et al. [170] and Espinosa et al. [184] discussed the advantages and the unfortunately prevailing limitations of the different pro-active strategies for sarcoptic mange control in wild Caprinae, including the sustained culling of infected individuals, the substantial manipulation of host density and mass acaricide treatments via the oral route (e.g., in salt licks or medicated pellets).

With regards to drug delivery in authentic free-ranging wildlife exposed to *Sarcoptes* infection, successful results have been documented in a handful of controlled trials involving groups or small-sized populations of primates, carnivores and marsupials [185]. Testing of administration routes other than the oral one (e.g., via "burrow flaps" in wombats) is also underway [185]. However, a matter of concern is represented by the potential environmental effects of the mass administration of macrocyclic lactones (mainly ivermectin), as per common practice in game ungulate populations in Spain [170]. On the other hand, game treatment would limit venison consumption, due to the long ivermectin withdrawal time in edible tissues. Based on current evidence, whether to apply individual or mass treatments to free-ranging populations should be considered very carefully and avoided where not absolutely warranted [186].

23.3 Sarcoptic Mange in Domestic Animals

23.3.1 Sarcoptic Mange in Dogs

The primary host of *S. scabiei* var. *canis* is the dog but this variety can infest other mammals [17]. Like in other hosts, sarcoptic mange is highly contagious and the transmission of mites occurs by direct host-to-host contact or by fomites. Cross-infection between different species was been reported also. Infected red foxes could be a source of *Sarcoptes* mites for domestic dogs, especially considering the increasing urban fox population in some countries. Breed or sex predilection was not reported but young dogs seem to be at higher risk. Immunocompromised dogs are more at risk of developing a severe condition. Dogs living in groups, roaming and hunting dogs or dogs living with homeless people are more frequently infected [187].

Several clinical forms are described. The classical form is characterized by intense pruritus, erythema, papules, crusts and patchy hair loss at the onset (Fig. 23.2a). Urticarial lesions are seen in about 30% of cases [16]. Secondary to pruritus: excoriations, erosions, crusts and lichenification are often observed. Bacterial or fungal infection is commonly observed. In the localized form the lesions are restricted to pinnal margins or lateral elbow and the pruritus is variable. Other areas can be touched but the back is spared most of the time. Some dogs only show mild pruritus and diffuse truncal scaling.

The Norwegian/crusted mange is a rare form characterized by thick yellow crusts on the face, lateral elbow and other parts of the body as well (Fig. 23.2b). The pruritus is mild to moderate. This form is seen in debilitated dogs, old dogs or dogs

Fig. 23.2 Lesions of sarcoptic mange in domestic animals. (**a**) A dog in France (courtesy of Parasitology dept, EnvA), (**b**) A stray dog with chronic infection in Romania (courtesy of Raluca Mindru), (**c**) A cat in Australia (courtesy of Richard Malik), (**d**) A sheep in France (courtesy of Parasitology dept, EnvA), (**e**) A goat in Italy (courtesy of Luca Rossi), (**f**) A rabbit in southern China (courtesy of Fang Fang), (**g**) A cow in Italy (courtesy of Luca Rossi), (**h**) A llama in Belgium (courtesy of Yannick Caron), (**i**) A pig in Italy (courtesy of Luca Rossi)

having received glucocorticoid for an extended period of time or at high dosage. In some cases, especially in chronic infections, systemic signs are reported: pyrexia, weight loss, anorexia and polyuria-polydipsia, the latter being associated with immune-mediated glomerulonephritis [17].

Differential diagnosis includes all other pruritic conditions such as other ecto-parasitic infections, atopic dermatitis and allergic skin diseases. Unlike allergic skin disease, in case of sarcoptic mange the pruritus escalates quickly [16]. Moreover, the pruritus is known to increase after a warm bath. These elements are not consistent, and complementary analysis is useful for the diagnosis. The pinnal-pedal scratch reflex is an easy to do and useful test: when positive, the rubbing and

scratching of the pinna provokes a movement of the hindlimb in an attempt to scratch the ear. A positive pinnal-pedal scratch reflex is present in 75% to 90% of cases; however, the reflex may be seen in other pruritic conditions [188].

Skin scraping can reveal the presence of the parasite (different stages of the mites or feces). Multiple skin scrapings are necessary and should be done on sites without excoriation; areas with papules and yellow crusts should be preferred. The ear margins and the lateral elbow are more likely to harbor the mites. The scrapings are observed microscopically in lactophenol or mineral oil. Negative skin scrapings do not exclude the presence of the parasite as only 20% to 50% of samples will be positive, depending on the number of skin scrapings.

ELISA testing is available for the diagnosis of sarcoptic mange in dogs. These tests use the detection of specific IgG and are reported to be sensitive and specific. Dogs with house dust mite sensitivity do not show cross reactivity whereas dogs with sarcoptic mange can have positive intradermal reactions or specific IgG or IgE against house dust mite allergens. In other words, a dog suffering from atopic dermatitis with a positive serological test for specific anti house dust mite IgE will not have a positive IgG serological test for sarcoptic mange. But a dog with sarcoptic mange may have a positive house dust mite specific IgE serological test or intradermal reaction [189].

Histological examination is rarely useful; unless mites are present in the skin sample it is not possible to conclude on the absence of sarcoptic mange based on a negative result. Most of the time, histological features are nonspecific and can lead to a false diagnosis of atopic dermatitis or allergic dermatitis.

In the case of sarcoptic mange, secondary bacterial or *Malassezia* skin infections can be diagnosed with cytologic microscopic examination (impression smears). Moreover, hematological, biochemical and urinalysis can be useful especially in chronic cases to search for signs of kidney damages (glomerulopathy). Underlying diseases must be investigated in case of Norwegian sarcoptic mange such as hyperadrenocorticism [16].

Trial therapy is recommended whenever sarcoptic mange is suspected in a dog, even if skin scrapings are negative, because positive identification of the mites is difficult [17]. The specific treatment includes the use of topical or systemic acaricides. In the past, amitraz dips or fipronil sprays were proposed. Nowadays, systemic treatments are preferred. They include the administration of macrocyclic lactones (selamectin, ivermectin, moxidectin or milbemycin oxime). Among them, selamectin and moxidectin are given as a spot-on formulation. Two administrations at one-month interval are recommended. Milbemycin oxime should be given orally and weekly for one month. Oral or subcutaneous ivermectin is effective but contraindicated in avermectin-sensitive canine breeds (with mutations on *MDR1* gene). Systemic treatment is also possible with isoxazolines (afoxolaner, fluralaner, lotilaner or sarolaner) which were proved to be highly effective with a single oral administration [190–192]. Using a metagenomic approach, Mindru et al. [193] demonstrated that the treatment with afoxolaner in 3 naturally-infected dogs had a significant impact on the skin microbiota. The microbial diversity significantly increased after the treatment and concomitantly the relative abundance of

Staphylococcus bacteria decreased. Similar observations were made in two studies about the modification of the skin microbiota in experimentally infected pigs or wild canids [194, 195].

23.3.2 Sarcoptic Mange in Cats

Feline cases of mange are usually caused by *Notoedres cati*, a mite species which belong to the same family (Sarcoptidae) as *S. scabiei* [16, 17]. Notoedric mange is primarily a disease of felids, but cases have also been reported in rodents, lagomorphs and occasionally dogs or foxes.

Sarcoptic mange has been reported infrequently in cats. In the literature, there are some individual cases [53, 54] and only one report of 25 simultaneous cases, suggesting transmission from cat to cat in a single household in Sweden [196]. Usually, the contact with an infected dog is documented. Sometimes, cats with sarcoptic mange simply reside in areas known to be frequented by infected wild animals (foxes or wombats in Australia). Pruritus is not a prominent clinical feature and cats with sarcoptic mange have advanced lesions reminiscent of crusted scabies with abundant mites in skin scrapings (Fig. 23.3c). Several therapeutic protocols have been tested, including topical administration of lime sulfur, subcutaneous injection of ivermectin and use of spot-on formulations (containing selamectin, moxidectin or fluralaner) [53, 197].

23.3.3 Sarcoptic Mange in Pigs

Sarcoptic mange, caused by *S. scabiei* var. *suis*, is a common disease which can significantly reduce growth, feed conversion and reproductive performance in pigs [121, 198]. Sarcoptic mange was reported in every country where pig farming is present and sometimes, serological surveys and investigations at slaughterhouse (with direct examination of skin samples) may reveal high infection rates [121, 199, 200].

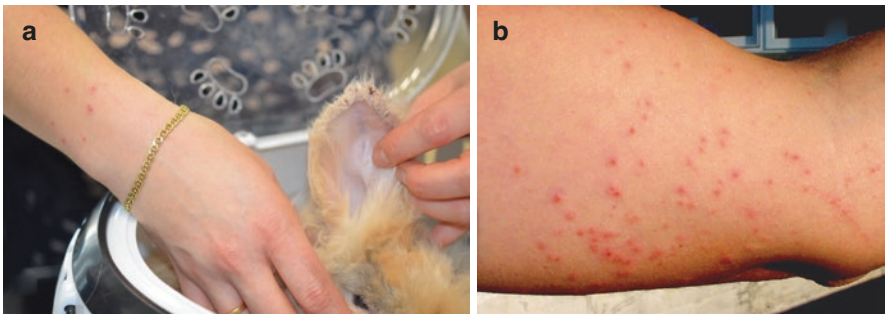

Fig. 23.3 Cases of human contamination with *Sarcoptes scabiei* mites from animals. (**a**) Contamination from a pet rabbit (courtesy of Parasitology dept, EnvA, France), (**b**) Contamination from a wild Northern chamois (*Rupicapra rupicapra*) (courtesy of Luca Rossi)

Pigs with a chronic form of sarcoptic mange are considered as the main reservoir of *Sarcoptes* mites in farms [201]. The transmission is mainly by direct contact. Piglets become infected primarily through contact with their mother. Horizontal contamination during the fattening period is limited and an infected pig is supposed to contaminate 0.06 congeners per day [202]. Animals reared on straw, a suitable substrate for parasite survival, are more at risk [120]. Poor overall farm hygiene and lack of acaricide treatments are also risk factors. A seasonal effect was described: more sarcoptic mange lesions have been detected at slaughterhouse inspection in winter and spring in South Australia [203].

Clinical signs include erythematous papules, particularly on the skin of rump, flanks, abdomen or ear base (Fig. 23.2i). Pruritus occurs between 2 and 11 weeks after infection and increases with hypersensitivity response. A chronic, hyperkeratotic form may develop in a few animals. The skin looks rough and thick, with adherent crusts containing *Sarcoptes* mites.

In pigs, differential diagnosis of sarcoptic mange includes foodborne parakeratosis, exudative epidermitis, deficiencies of niacin/biotin, smallpox, photosensitization, sunburn and insect bites [204]. Scratch and rub indexes were proposed to estimate the level of pruritus in pigs with sarcoptic mange. Scratching index (SI) is obtained by counting the number of scratching and rubbing episodes in a room or pen for 15 min, divided by the total number of animals. An index greater than 0.1 suggests the presence of *S. scabiei* mites and the need to revise the parasite control plan [205]. A lesion scoring system was proposed during slaughterhouse inspection [206]. Sarcoptic mange is considered to be out of control in a farm if the average score from the pigs is greater than 0.5. The sensitivity of this method is estimated at more than 98% for individual scores of 2 or 3 [207]. However, a recent study questioned the performance of lesion scoring system [208]. Definitive diagnosis of sarcoptic mange in pigs relies on the detection of *Sarcoptes* mites in skin samples. However, the sensitivity of direct examination is low, being estimated at less than 50%.

Several ELISA tests were developed for the diagnosis of sarcoptic mange in pigs [209]. One of them was developed using an extract of *S. scabiei* var. *vulpes* as an antigen [210]. The specificity of the test is excellent, above 98% [211], but the sensitivity is only 50% and 80% in sows and piglets, respectively. Antibodies are detectable 5 to 7 weeks after infection and persist for 9 to 12 months. Kessler et al. [212] showed that the sensitivity of tests developed from *S. scabiei* var. *suis* antigens was better. Beyond the determination of the status of a farm, serological tests may be used to assess the efficacy of control measures.

Injectable macrocyclic lactones (doramectin and ivermectin) are labeled for use in many countries and are considered as highly effective treatments. A second administration at a fortnight interval may be necessary in some cases. Topical treatment may also be used in pigs with sarcoptic mange: lime sulfur dips repeated at intervals of 3 to 7 days, phosmet or permethrin sprays (once or twice, respectively). Very recently, oral afoxolaner (a new acaricide from the isoxazoline family) was demonstrated to be highly effective for the treatment of sarcoptic mange in experimentally-infected pigs [187] but also in a pig used as a companion animal [213].

23.3.4 Sarcoptic Mange in Domestic Herbivores

In cattle, sarcoptic mange, caused by *S. scabiei* var. *bovis*, is considered as one of the most severe skin diseases [214, 215]. All breeds may be affected even though some seem more susceptible than others. Clinical signs start on the head and the neck. The skin is erythematous, congested and edematous with typical skin folds (Fig. 23.2g). Hyperkeratosis is usually moderate. Skin lesions spread rapidly and, in the absence of treatment, the entire body surface may be affected after only 2 to 4 weeks. Pruritus is intense and almost permanent. This can lead to severe self-inflicted skin lesions. Bacterial infections are often observed. Sarcoptic mange has a marked effect on feed ingestion and infected cattle have usually a very poor body condition. Very severely affected animals may die. Differential diagnosis includes psoroptic and chorioptic mange and other pruritic nonparasitic skin conditions. Microscopic examination of deep skin scrapings may confirm the clinical diagnosis. However, the number of mites is usually low.

In sheep, sarcoptic mange, caused by *S. scabiei* var. *ovis*, is considered as a rare disease in Western Europe but may be common in other parts of the World [214, 215]. It is characterized by the development of thick adherent crusts mainly located on the hairy parts of the body and more particularly on the head (around the eyes and on the muzzle) (Fig. 23.2d). Pruritus is moderate and body condition is not affected except if the vision is limited by the presence of crusts. Orf (a viral contagious and zoonotic disease of sheep) must be included in the differential diagnosis. Psoroptic mange (sheep scab) is a common severe disease of sheep worldwide but lesions are limited to the wooly skin surface. Chorioptic mange is also common but is considered as a mild condition and lesions are limited to the legs and scrotum in rams.

In goats, sarcoptic mange is a severe disease which may lead to very poor body condition and even death [214, 215]. Like in cattle, lesions are first detected on the head and neck (Fig. 23.2e). Hyperkeratosis is marked and very thick and adherent crusts develop. Hair loss is extensive and generalization is the rule. Diagnosis is usually straightforward based on clinical signs.

Several drugs are available for the treatment of sarcoptic mange in cattle, sheep and goats. Some must be applied topically (like organophosphates, carbamates and pyrethroids) and others with a systemic activity (macrocyclic lactones) are given orally or through a subcutaneous injection. However, macrocyclic lactones (which have a wide spectrum of activity against mites, insects and nematodes) act fairly slowly on parasitic mites. It means that treated animals remain contagious for at least 5 days post treatment. Pour-on formulations of macrocyclic lactones are available in cattle but due to the fairly poor pharmacokinetic performances of these formulations it is recommended to administer the drug subcutaneously whenever possible.

In **dromedaries** (*Camelus dromedarius*), sarcoptic mange is commonly observed [104]. The lesions first develop on the abdomen, the hind legs and the groins. These

lesions are highly pruritic. The intense scratching behavior rapidly induces a marked exudation and secondary bacterial infections are common. There is a rapid extension of the lesions to the entire body surface and, in the absence of treatment, the animals may die in 2 to 3 months.

In New World domestic camelids, **llamas** (*Lama glama*) and **alpacas** (*Vicugna pacos*), sarcoptic mange is regularly reported [216]. In these animals, the disease may lead to very poor body condition and even death. Furthermore, treatment is always extremely difficult and protracted. Lesions consist in very thick and adherent crusts initially located on the face and neck but generalization is the rule (Fig. 23.2h). Pruritus is systematically present. It is noteworthy that other mite infections due to *Psoroptes* and *Chorioptes* spp. are common in New World camelids. *Psoroptes* mite species are responsible for a severe ear infection whereas *Chorioptes* mites develop mainly on the lower parts of the legs. Mixed infections are possible.

Macrocyclic lactones represent the best treatment option for sarcoptic mange in camelids. It is mandatory to use injectable formulations. In dromedaries, macrocyclic lactones should be administered two to three times at weekly or fortnightly intervals. In New World camelids, treatment is difficult and several injections (up to 10!) are required [108, 217].

In **horses and donkeys**, sarcoptic mange is caused by *S. scabiei* var. *equi*. In the past, the infection was particularly important during wartime in cavalry due to its high contagiousness (through direct or indirect contacts), its severity and the paucity of treatments which were difficult to administer, often potentially toxic and very time consuming. Under such conditions, it is not surprising that sarcoptic mange was considered as one of the most important diseases of horses and that old textbooks gave a lot of emphasis to the condition, its prevention and treatment. Fortunately, equine sarcoptic mange was eradicated from most European countries through appropriate animal health regulation schemes. The disease starts on the head and neck like in cattle. Generalization is rapid and, in the absence of specific treatment, the general condition of infected horses deteriorates rapidly [218]. Mane and tail hair are usually spared. Other parasitic mites are found in horses: *Psoroptes equi* affecting the mane and tail hair and *Chorioptes equi* mainly located on the lower parts of the legs.

In rabbits, sarcoptic mange is caused by *S. scabiei* var. *cuniculi*. The mite is considered as one of the most common ectoparasites of rabbits. Sarcoptic mange is responsible for major production losses (associated with weight loss or death) in rabbit farms in all the countries where this type of animal production is present [219, 220]. The disease is regularly reported in pet rabbits. Cutaneous lesions, which include alopecia and crusts, usually develop first on the head and later on the paws (Fig. 23.2f). Sarcoptic mange in rabbit is highly pruritic. Self-mutilation may lead to wounds and secondary bacterial infection. Some infected rabbits become lethargic and can die within a few weeks.

23.4 Cross Infections and Risk of Human Contamination from Animals

Natural cross infections have been reported between different animal species but also from animals to humans (Table 23.2). Neveu-Lemaire [221] established a first list of cross transmission of *S. scabiei* varieties between different hosts in natural conditions. Further studies demonstrated that experimental contamination was possible using *S. scabiei* mites from goats to camels, sheep [105, 229] and chamois [233]. Mites collected from dogs were able to develop in rabbits permanently, and in ruminants, pigs and cats for a limited period of time (1 to 3 months) [133]. Animal *Sarcoptes* strains which infect humans usually come from dogs. It is estimated that a zoonotic transmission occurs in 25% to 30% of the cases of canine sarcoptic mange [16]. Transmission to humans resulting in a transient infection was reported also from a wide range of domestic animals (cats, pigs, camels, horses, goats, sheep, rabbits, ferrets and llamas) but also from wild animals (chamois, red foxes, wombats, lions and bears) (Table 23.2). The human *S. scabiei* variety is however more easily transmitted between humans and is generally responsible for a more clinically severe disease for humans as compared to animal-derived varieties. As a consequence, human scabies must be treated, whereas zoonotic scabies is a transient and self-limiting condition (Fig. 23.3). In literature, there is only one example of a permanent human infection in a 14-year-old girl in contact with three dogs with extended lesions of sarcoptic mange. The girl developed a crusted scabies and

Table 23.2 Reported cases of *Sarcoptes scabiei* cross-infection between different mammalian species

	to humans	to dogs	to rabbits	to pigs	to sheep	to goats	to horses
from humans							Neveu-Lemaire et al. 1938
from dogs	Neveu-Lemaire 1938, Emde 1961, Beck 1965, Smith and Claypoole 1967, Charlesworth & Johnson 1974, Aydingöz & Mansur 2011		Arlian et al. 1984	Arlian et al. 1984		Arlian et al. 1984	Neveu-Lemaire 1938
from rabbits							
from pigs	Neveu-Lemaire 1938, Chakrabarti 1990, Grahofer et al. 2018						
from sheep	Neveu-Lemaire 1938	Neveu-Lemaire et al. 1938				Neveu-Lemaire 1938, Abu-Samra et al. 1984	
from goats	Neveu-Lemaire 1938, Salifou et al. 2013			Neveu-Lemaire 1938	Neveu-Lemaire 1938		Neveu-Lemaire 1938
from horses	Neveu-Lemaire 1938						
from llamas	Neveu-Lemaire 1938				Neveu-Lemaire 1938		Neveu-Lemaire 1938
from wild animals	**Red foxes, water bufaloes, chamois** Neveu-Lemaire 1938, Chakrabarti et al. 1981, Menzano et al. 2004	**Red foxes**: Samuel 1981, Bornstein 1991, Soulsbury et al. 2007					**Red foxes**: Neveu-Lemaire 1938

further contaminated several members of her family. Mites collected from the girl were successfully inoculated to a naive dog but experimental infection failed in rabbits or nude mice [234]. Estes et al. 235] observed that *S. scabiei* var. *canis* females could make galleries and lay eggs in the skin of an experimentally infected human.

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Management of Common Scabies

24

Dev Tilakaratne, Nicholas De Rosa, and Bart Currie

24.1 Introduction

This chapter covers the commonly accepted anti-parasitic agents for common scabies, as well as the treatment of secondary bacterial infection, dermatitis and pruritus, which frequently accompany common scabies. Furthermore, it will address the non-pharmacologic interventions that are important in minimising treatment failure and spread of the infestation to others.

Before discussing the treatment options, it is important to clarify the basis upon which the decision is made to begin treatment. The numerous factors that hamper the diagnosis of scabies mean that patients often present to the clinician with a suspicion of scabies, rather than a firm diagnosis. The 2020 International Alliance for the Control of Scabies (IACS) Consensus Criteria for the Diagnosis of Scabies may also help guide treatment by stratifying the confidence of the diagnosis and by classifying patients as either confirmed scabies, clinical scabies or suspected scabies [1]. It obviously follows that treatment is mandated if patients have confirmed scabies or clinical scabies. However, it is not uncommon for clinicians with limited knowledge of skin conditions to make a diagnosis of suspected scabies in patients who may have a history of itch and lesions in a typical distribution, but in whom there is actually another diagnosis. When there is uncertainty, the most important pointer for making a diagnosis of scabies and instituting a trial of empirical anti-scabietic therapy is that the patient has an epidemiological link to family members with scabies or resides in a community with endemic scabies. Therefore, in patients

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who may have scabies but who may also have an alternative diagnosis, the decision for a trial of empirical therapy is at the discretion of the clinician. Factors that may influence clinicians to treat for scabies without a firm diagnosis include:

- The consequences of missing a diagnosis of scabies, such as concomitant group A streptococcal infection, with potential for systemic and immunological sequelae.
- The local prevalence of scabies.
- The generally well-tolerated nature of treatments for scabies making the response (or lack thereof) to treatment a relatively harmless diagnostic test.
- The difficulty in visualising mites, mite products and burrows for an untrained examiner and the relative ease in using representative heuristics to make the diagnosis (diagnosing scabies if a patient with severe itch fits the typical demographic of a person with scabies presenting to that institution).

The authors recommend that clinicians invest the time, resources and effort into making a diagnosis of confirmed scabies or clinical scabies according to the 2020 IACS criteria to prevent misdiagnosis and incorrect treatment. In such a situation, there is also the risk that ongoing itch is misattributed to post-scabietic itch, which further delays diagnosis and treatment of their true condition.

Topical anti-parasitic treatments for common scabies include permethrin, sulphur, crotamiton and benzyl benzoate (alone and in combination with tea tree oil). Topical lindane and malathion are included for a historical perspective but are not recommended options. Oral treatments include ivermectin.

A recent systematic review of scabies treatments suggests that combination therapy comprising oral ivermectin and topical permethrin has a superior cure rate at 3 to 6 weeks post-treatment compared to monotherapy with any topical or oral agent [2]. The efficaciousness of combination therapy is also supported by the finding that the use of benzyl benzoate without adjunctive topical or oral treatment, a single treatment with oral ivermectin instead of 2 or more treatments, and the failure to decontaminate furniture have been identified as risk factors for treatment failure [3].

24.2 Permethrin

Permethrin is a photostable synthetic pyrethroid discovered in the late 1940s. It was subsequently developed for veterinary and agricultural use due to its low mammalian toxicity and high insecticidal activity. It has scabicidal activity but no clinically reliable ovicidal activity, so the accepted treatment regimen is 2 applications administered 1 week apart to kill the adult mites, larvae and nymphs with the first treatment, and recently hatched larvae and nymphs with the second application. It had been used in the veterinary and agricultural settings for decades before being considered for treating humans with ectoparasitic infestations, initially as a 1% cream for pediculosis capitis and subsequently as a 5% cream for common scabies. The first randomised, double-blinded controlled trial using permethrin 5% cream was

performed in the Republic of Panama in 1986, where scabies had long been endemic. The comparator was lindane (gamma benzene hexachloride) 1% lotion. Adults and children as young as 2 years of age were included in the study. Treatment consisted of a single application of the investigational product, applied head to toe and left on for 8 to 12 h before being washed off with soap and water. The results demonstrated a 91% cure at 4 weeks in the permethrin cream group compared with 65% in the lindane lotion group, where cure was defined as the absence of new lesions and having negative skin scrapings for mites or mite products under microscopy. This was a paradigm shifting study as it provided an alternative to lindane, which was, in many places, the most readily available treatment. It was only decades after the introduction of lindane in 1948 that the rare but potentially fatal central nervous system (CNS) toxicity associated with repeated or excessive application became apparent [4].

Since that time, there have been numerous randomised controlled trials involving topical permethrin. A recent systematic review of anti-scabietic agents, which included 30 randomised controlled trials involving topical permethrin, demonstrated that topical permethrin was significantly more effective at achieving cure at both 1–2 and 3–6 weeks compared with topical lindane, topical crotamiton and oral ivermectin [2]. The direct meta-analysis conducted in this review also demonstrated superiority of topical permethrin over benzyl benzoate at 1 to 2 weeks; however, this was only significant when including studies with suboptimal dosing of benzyl benzoate (one application only), and was non-significant in individual studies comparing more than one application of permethrin and benzyl benzoate [2].

Whole body application with a thin layer of permethrin 5% cream is recommended, with a repeat application 7 days later. Due to the predilection for scabies to burrow at acral sites, especially distal limb flexural areas, toes and fingers, it is recommended that special care is taken to ensure adequate application to these regions. Special care is to also be taken to ensure the product is applied to areas that can be hard to reach or easily missed, such as external genitalia and associated creases, under nails and on the back and buttocks. Although it is true that scabies mites are much less likely to infest the scalp and face in adults compared with children, involvement of these areas has been reported, especially in tropical climates. Therefore, the authors recommend treating these areas as well. For individuals with a larger body surface area, more than one standard 30 g tube of cream may be required to achieve a thin layer over the whole body.

Permethrin has an established record of having an excellent safety profile in adults. In a Cochrane database systematic review of ivermectin and permethrin, it was found that across 502 participants in 4 studies, 4% of participants treated with permethrin had an adverse event, with no withdrawals due to adverse events reported [5]. In October 2019, severe immediate hypersensitivity with generalised contact urticaria to permethrin cream (confirmed by repeat open application testing of permethrin cream) was described in a case report, demonstrating that severe adverse effects to permethrin are possible, even if exceedingly rare [6]. The most commonly reported reaction to permethrin cream is irritant dermatitis.

Permethrin is considered safe for use in pregnancy. [7, 8] A retrospective controlled cohort study of 196 women who were treated with permethrin during pregnancy did not show an increased risk of adverse pregnancy outcomes [9]. It has been assigned to pregnancy category B by the United States Food and Drug Administration (FDA). It is unknown whether permethrin is excreted in breast milk; however, permethrin is considered the preferred treatment for scabies during lactation [10].

24.3 Topical Sulphur

Topical sulphur is one of the oldest reported treatments for scabies. It was described as a 5-day treatment for scabies by Saint Hildegaard von Bingen, a Benedictine nun, in her book on health titled 'Causae et Curae'. Sulphur is not active against scabies mites in vitro; its anti-scabietic activity may be secondary to an active compound, possibly pantothenic acid, that is produced when it is applied to the skin [11].

Although earlier studies suggested sulphur may be as efficacious as other topical treatments for scabies [12], a recent meta-analysis found sulphur to have significantly lower cure rates than permethrin and higher rates of adverse events than other anti-scabietic agents [2].

A variety of preparations and treatment regimens have been utilised. A 10% ointment has commonly been used in adults, with lower concentrations of 5% to 10% for children and infants. Treatment courses vary significantly, ranging from 3 to 21 days. The authors recommend that the ointment be applied over the whole body daily (excluding eye and oral mucosa) and left on overnight for 3 to 5 nights and then repeated after 7 to 10 days. Longer courses are associated with a higher risk for adverse events.

Sulphur is relatively cheap and may be considered in situations where cost limits other options, although its cost-effectiveness to treat one case has been shown to be poor [13]. Disadvantages of topical sulphur include it being messy and malodorous, it can stain clothing and bedding, and it may produce irritant dermatitis [12], particularly in humid climates. Importantly however, it is considered safe for use in infants and pregnant women, [7, 8] despite there being no published studies on its use in pregnancy. It is classified as FDA pregnancy category C. It is likely safe for use during lactation [7], although there is a lack of clinical data to support this.

24.4 Crotamiton

Crotamiton was first reported as an effective treatment for scabies in the late 1940s [14]. Its mechanism of action is unknown. Crotamiton is applied as a 10% cream or lotion in adults, infants and children. It should be applied over the whole body (excluding eyes and oral mucosa) daily for 2 to 5 days and the previous days application should not be washed off until before the next dose. If new lesions appear or itch persists for more than 2 to 4 weeks (or 7–10 days in children) after initial

treatment then re-treatment can be given, although alternative therapeutic options should be considered [15].

Systematic reviews have shown permethrin cream to be superior to crotamiton in minimising treatment failure and in relieving itch. [2, 16] Crotamiton appears to be as effective as lindane and other topical agents. [2, 16]

Skin irritation is an uncommon adverse reaction to crotamiton and allergic contact dermatitis has rarely been reported [15]. A case of Hailey-Hailey disease (benign familial pemphigus) deemed secondary to crotamiton induced contact dermatitis has been described [17]. There are no animal or human studies examining the safety of crotamiton in pregnancy and breastfeeding, although no adverse outcomes have been reported and it is considered safe pregnancy. [7, 8, 15] It is classified as FDA pregnancy category C. Crotamiton is often prescribed in infants and small children due to its low toxicity profile, although permethrin is increasingly being used in ages 2 months and older. In instances where permethrin cream is unobtainable, crotamiton may be a useful and cost-effective alternative [12].

24.5 Benzyl Benzoate ± Tea Tree Oil

Benzyl benzoate was recognised as a treatment for scabies in the 1930s and was the first alternative to sulphur [18]. It is currently one of the most used topical agents in developing countries. Benzyl benzoate is not available in the United States.

It has been tested in solutions ranging in concentration from 10% to 25% and in various dosing regimens. Randomised controlled trials comparing oral ivermectin with benzyl benzoate have provided mixed results, likely due to the differing treatment regimens in the studies [16]. Benzyl benzoate is considered as effective as crotamiton, lindane and sulphur [16]. It is uncertain as to whether benzyl benzoate is as effective an anti-scabietic as permethrin. A recent meta-analysis suggests permethrin may have a higher cure rate at 1 to 2 weeks compared to benzyl benzoate [2], although this meta-analysis included comparative studies with sub-optimal, single applications of benzyl benzoate. The two studies included in the meta-analysis with repeated dosing of benzyl benzoate found no significant differences in cure rates as compared to topical permethrin, both individually and with pooled data. [13, 19]

Skin irritation is a common side effect of benzyl benzoate and can be intense in the first few minutes after application. A stinging or burning sensation and dermatitis have commonly been reported as adverse events in studies. Benzyl alcohol, a metabolite of benzyl benzoate, has been associated with neonatal fatal intoxication (‘gasping syndrome’) when used to rinse venous catheters [7], although this has not been reported with topical use. A retrospective matched-cohort study examining 444 pregnant women treated with benzyl benzoate found no evidence of adverse pregnancy events [9]. Benzyl benzoate is generally considered safe for use during pregnancy [7, 8] and is classified as FDA pregnancy category C, although permethrin is still preferred in this setting.

The treatment dose recommended by the authors is benzyl benzoate 25% emulsion applied over the whole body (excluding eyes and oral mucosa) and left on for 24 h, with reapplication to the hands if they are washed. The solution should be diluted with 3 parts of water for children between 6 months and 2 years and diluted with equal parts water for children aged 2 to 12 years. The treatment should be repeated in 7 days.

Although scabies was not considered endemic to Indigenous Australia prior to European colonisation, the essential oil of the tea tree was used as a traditional medicine by Aboriginal Australians for treatment of bruises, insect bites and skin infections [20]. It rapidly kills *S. scabiei* in vitro [21] and has been successfully used topically mixed with benzyl benzoate and in combination with oral ivermectin in refractory crusted scabies [22]. Tea tree oil may be added in a concentration of 5% to benzyl benzoate.

24.6 Oral Ivermectin

Ivermectin is a semi-synthetic avermectin, which are a highly active broad-spectrum anti-parasitic drugs isolated from fermentation broths of *Streptomyces avermitilis* [23]. The 2015 Nobel Prize in Physiology or Medicine was awarded to William C. Campbell and Satoshi Ōmura for their discovery of avermectin [24]. Ivermectin has been used in humans since the mid-1980s, most commonly for the treatment of the filarial worms *Onchocerca volvulus* (the cause of river blindness), *Wuchereria bancrofti* and *Brugia malayi* (causing filariasis), and is the drug of choice for strongyloidiasis and cutaneous larva migrans [11]. Ivermectin acts by binding to glutamate-gated chloride ion channels and altering chloride channel function, resulting in paralysis and death of nematode and arthropod parasites [25]. Glutamate-gated chloride ion channels belong to a group of receptors that include the human gamma-aminobutyric acid (GABA) receptor and while ivermectin has modulatory effects at this receptor [26], it does not penetrate the CNS of mammals and thus does not interfere with mammalian GABA-dependent neurotransmission [23]. Although CNS toxicity is documented in certain dog varieties, its extensive use in filarial programs has shown few adverse reactions [11]. Ivermectin does not have ovicidal action which may result in treatment failure with single oral doses due to hatching of ova and development of new mites.

Ivermectin has been studied in doses ranging from 100 to 200 μg/kg. A 2007 systematic Cochrane review of interventions for scabies found oral ivermectin to be superior to placebo and lindane, and less effective than topical permethrin [16]. In comparison with benzyl benzoate there was significant heterogeneity of results. A more recent systematic Cochrane review directly compared permethrin and ivermectin (topical or oral) in treating scabies [5] and included 15 studies with 1896 participants, the majority conducted in South Asia or North Africa. It is worth noting the risk of bias was deemed to be moderate and reporting in many studies was considered poor. They found that oral ivermectin at a standard dose of 200 μg/kg may lead to slightly lower rates of complete clearance after 1 week compared to permethrin 5% cream, but by week 2 there may be little or no difference. After 4 weeks with 1 to 3 doses of either medication there was little or no difference in

rates of clearance. They also found that after 4 weeks there is probably little or no difference in rates of clearance between systemic and topical ivermectin (as a 1% lotion) as well as between topical ivermectin and permethrin cream.

In the above studies, only a handful of adverse events were reported including headache, abdominal pain and vomiting, with no study withdrawals due to adverse events. There has been a report of neurotoxicity occurring in a cohort of elderly patients [27] although there is discussion as to the validity of the report [16]. Ivermectin has been used extensively in filarial programs with excellent tolerance. There is limited safety data on its use in children younger than 5 and during pregnancy and lactation, and it is therefore not recommended for use in these groups. It is FDA pregnancy category C. It has been shown to be teratogenic in animal studies at high doses that were toxic to the pregnant female, making it difficult to draw conclusions about teratogenicity at usual treatment doses. No adverse pregnancy outcomes have been reported in humans, [7, 8] although clinicians continue to avoid its use due to the presence of safer alternatives. Ivermectin enters breast milk and its safety has not been established in children. Some authors therefore recommend it should be avoided during lactation [28], although others note it may be considered for use in lactating mothers when topical options have failed [10]. Drug resistance is a concern with acaricides and clinical resistance to ivermectin has been documented, with in vitro confirmation, in two persons with crusted scabies after multiple doses of ivermectin [29].

Oral ivermectin is safe and simple to administer and treats the entire skin surface without the risk of missing areas of infection, which can occur when applying topical products. One study found ivermectin to be more cost-effective than permethrin in treating scabies [13]. For classic scabies, the authors recommend an initial dose of oral ivermectin of 200 μg/kg with food, repeated once after 8 to 15 days.

24.7 Lindane

Lindane is the commercial purified form of the organochlorine chemical gamma benzene hexachloride. It has been used agriculturally as an insecticide as well as in the treatment of lice and scabies. There have been reports of neurotoxicity [30–32], convulsions [33] and aplastic anaemia [34], and it has consequently been banned for agricultural and medicinal use in many Western countries. There have also been reports of mite resistance to lindane [35].

For the treatment of scabies, it has mainly been used in a 1% preparation. A Cochrane systematic review found permethrin cream to be superior to lindane for the treatment of clinically diagnosed scabies, although in a subgroup of participants with microscopically confirmed scabies there was uncertainty as to its superiority [16]. Permethrin also appeared to be better at relieving itch than lindane. The review found that lindane appeared to be less effective than oral ivermectin, but no significant differences were found in treatment failure between lindane and crotamiton or sulphur. Lindane is FDA pregnancy category C and should not be used in pregnancy due to potential neurotoxicity [7]. It should be avoided during lactation as it is excreted in breast milk and can result in infant seizures and elevated liver function tests [10].

Due to the aforementioned potential for significant adverse effects and the availability of other safe and efficacious treatment options, the authors do not recommend lindane for the treatment of scabies.

24.8 Malathion

Malathion is an organophosphate pediculicide and acts via irreversible anticholinesterase inhibition. There are no clinical trials investigating the efficacy of malathion in treating scabies. It is unlikely that further studies will be forthcoming as malathion has been classified as probably carcinogenic in humans [36]. It should be avoided in the treatment of scabies.

24.9 Treatment of Secondary Bacterial Infection

Secondary bacterial infection of scabies lesions is common and can result in bacterial pyoderma or bacterial sepsis. *Streptococcus pyogenes* and *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus*) are the most common infecting organisms, although any bacteria colonising the skin may be involved. [11, 37, 38] Streptococci and staphylococci have been isolated from mite faecal pellets and from skin burrows, signifying the possibility of mites causing bacterial spread [11]. Identification and early treatment of secondary infection is important to prevent complications of bacterial sepsis and post-streptococcal glomerulonephritis. Treatment of secondary bacterial infection may take the form of topical or oral antibiotics and may be accompanied by adjunctive bleach baths or potassium permanganate soaks. Swabs of infected sites not responding to empirical therapy should be sent for microscopy, culture and sensitivity to guide further antimicrobial choice.

Suitable empiric anti-bacterial medications include isoxazolyl penicillins (e.g. dicloxacillin 500 mg four times per day) or first generation cephalosporins (e.g. cephalexin 500 mg four times per day) for a 7-day treatment course. Short course oral co-trimoxazole (4 mg/kg plus 20 mg/kg twice daily for 3 days) has been shown to be as effective as intramuscular benzathine benzylpenicillin in treating impetigo in Indigenous Australian children, of which 17% of those treated had concurrent scabies infection [39]. The findings from a recent systematic review also suggest that co-trimoxazole is effective for the treatment of impetigo, purulent cellulitis and abscess and wound infection, while beta-lactam antibiotics remain the treatment of choice in non-purulent cellulitis [39].

24.10 Treatment of Associated Dermatitis

Treatment of the associated dermatitis may take the form of emollients and soap-substitute washes and, if more severe, may necessitate topical corticosteroids. In the opinion of the authors, the use of topical corticosteroids early in the treatment of

scabies may diminish the signs and symptoms of infestation, thereby masking treatment failure.

24.11 Treatment of Pruritus

Pruritus management usually takes the form of treatment of the scabies infestation itself. However, post-scabietic itch can be prolonged and severe and may require specific treatment. Determining whether prolonged pruritus is due to post-scabietic itch or scabies treatment failure can be difficult, especially when clinicians are not trained in the use of dermoscopy or the collection and interpretation of skin scrapings.

Crotamiton is a scabies treatment option that also has anti-pruritic effect. Any associated dermatitis should be adequately treated to reduce itch. If patients have debilitating pruritus interfering with concentration and sleep, then oral antihistamines may help, sometimes deliberately used with sedating properties to facilitate restful sleep.

24.12 Household Management

Household management is an essential component to the management of any patient with scabies. The main route of transmission of mite infestation is via skin to skin contact, although fomite-based transmission also occurs, and can result in re-inoculation of the same individual or other household members, who can then cause circular re-infestation within the household. The treatment of contacts is therefore an essential part of management to prevent re-infestation and ensure successful therapy.

Environmental decontamination is also important to prevent fomite-based disease transmission. Porcine models have been studied to assess the effectiveness of different decontamination measures [40]. It is recommended to wash clothes, towels and bedding (preferably on a hot cycle), and/or subject them to heat from an iron or a hot clothes dryer. Alternatively, they can be stored in a sealed plastic bag for 8 days as the mites, including those that subsequently hatch from eggs, are unlikely to survive longer than 7 days away from a host.

24.13 Primordial Factors

Primordial prevention strategies are the social, economic and environmental initiatives that can be undertaken to reduce the risk of scabies [41]. Epidemiological risk factors for scabies infestation include poverty and resultant overcrowding, sexual transmission and demographic forces such as migration, wars and population displacement. Addressing these social determinants of health are likely to have a significant impact on scabies transmission and infection at individual and societal levels, although there is a lack of evidence to guide such environmental interventions [42]. Improvements in living conditions are addressed through economic development, policy and regulatory changes. [43, 44]

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Management of Severe and Crusted Scabies

25

Dana Slape, Russell Thompson, and Erin McMeniman

25.1 Introduction

Crusted scabies is a profuse and florid hyperinfestation of scabies, usually seen in immunocompromised individuals with complex health issues, sensory deficits and mobility impairments. It is more infective than classic scabies due to the higher number of mites, often thousands to millions, which contrasts with classic scabies which may be an infection of 10 to 15 mites [1, 2]. Mites can survive for up to 7 days in exfoliated hyperkeratotic debris [3], and shedding of this highly infective hyperkeratotic debris and fomite transmission is an additional risk factor for community propagation to contacts [4]. However, it is primarily skin-to-skin contact which is the main modality of transmission of scabies including crusted scabies [4]. It may be weeks before the secondary contact manifests signs and symptoms of classic infection and may occasionally remain asymptomatic [5, 6]. In cases of repeated exposure, clinical symptoms and signs may be brisk, but with previously

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unexposed people, presentations of classic/simple scabies can take up to 6 weeks [7]. During this time, if left untreated, ongoing transmission to close contacts is a risk.

Delayed diagnosis of severe scabies and crusted scabies is common, attributable to the broad differential diagnosis and relatively uncommon incidence [8–10]. Worldwide prevalence of crusted scabies is uncertain, and although there is a greater understanding of the prevalence of classic scabies, this too remains uncertain [11]. Affected individuals often live with physical and cognitive disabilities, are chronically unwell and may be living in supported care facilities including residential aged care facilities or disability group homes (see Chap. 16).

Effective management of crusted scabies is a multi-disciplinary and long-term process that can be labour intensive, demanding of resources and with high direct and indirect economic costs [5, 12]. This includes treatment of the individual, environmental risk management strategies including contact tracing and treatment, and community-based surveillance and rehabilitation programmes to monitor for disease recurrence, complications and restoration of the patients' functional status to their baseline [13].

While there is no randomised control robust evidence for treating contacts as a method of reducing spread of classic scabies [4], it is an accepted recommendation that contact tracing and treatment is performed due to the high transmissibility and infectivity of this specific highly infectious variant [4]. Aggressive contact tracing and treating of contacts may result in reduction of the likelihood of community transmission and reduction of complications.

25.2 Management of the Individual Patient with Crusted Scabies

Multi-modal and multi-disciplinary management is required for severe and crusted scabies [6, 13–15]. The layers of hyperkeratosis harbour mites and prevent effective penetration of topical agents, and such patients need systemic therapy. The life cycle of the mite necessitates sequential therapeutic strategies. For the individual patient, keratolytic therapies, topical and oral anti-parasitic agents need to be combined, and early identification and treatment of complications is required. A rapid and effective public health strategy needs to be enacted including input from nursing, social work and other medical staff.

There remains a lack of standardised international consensus guidelines for both management of crusted scabies as well as management of associated outbreaks [12, 16]. International Centers for Disease Control guidelines [15] and European guidelines [14] have been informed by extensive work across tropical remote Northern Australia [13, 17–19], where the prevalence of crusted scabies is

thought to be the highest in the world at 2.4 per 1000 people [13]. Formal protocols may be variable between well-resourced settings and developing communities with limited access to best practice treatments but require management of this serious and contagious chronic disease. Aggressive multi-modal topical and systemic treatment is required as crusted scabies is recalcitrant to topical scabicidal monotherapy [15, 17, 20].

Severe and crusted scabies management is challenging: the patient themselves live with predisposing polymorbidity, the condition is rare, diagnosis is often delayed and complications are common and disabling. Furthermore, there is an extreme mite burden on the patient's rapidly exfoliative hyperkeratotic debris, drug penetration through thickened skin is inadequate and impaired skin integrity leads to secondary infection and high mortality. Keratotic debris bears a high mite burden and acts as a fomite for contacts and management of environmental decontamination can be inconsistent [12].

25.3 Identification of People with Crusted Scabies

Clinical suspicion is a prerequisite to confirming the diagnosis of crusted scabies and lack of awareness of this rare condition contributes to frequent misdiagnosis and delay of appropriate care. The risk factors shown below in Table 25.1 need to be recognised and addressed as part of a successful management plan.

Table 25.1 Risk factors (see detail in Chap. 17)

Immunosuppression
Topical and systemic iatrogenic immunosuppression
Acquired immunodeficient states, i.e., HIV, haematological malignancies
Congenital immunodeficiency
Transplant including haematological and solid organ
Connective tissue and rheumatologic immune disorders
Defective cutaneous sensation
Leprosy
Diabetes mellitus
Burns
Chronic congenital dermatoses
Physical immobility/disability
Quadriplegia/hemiplegia/paraplegia
Elderly
Bedbound
States of cognitive/intellectual/mental disability
Dementia
Down's Syndrome
Mental/cognitive/learning disabilities
Substance misuse disorders
Other risk factors:
environmental: overcrowding, sanitation, hot/humid/tropical environments, first nations peoples, developing and resource-poor settings
First Nations Peoples

25.4 Challenges with Clinical Diagnosis (See Detail in Chap. 17)

There is no standardised diagnostic algorithm for the diagnosis of severe/crusted scabies [21]. When clinical features are typical for severe or crusted scabies, the diagnosis can be readily identified by expert clinicians. However, clinical features may be protean with a broad list of differential diagnoses that may mimic more common dermatoses (see Chap. 17). Presentation can be localised or diffuse even extending to erythroderma and is usually associated with psoriasiform hyperkeratotic grey–yellow-cream-coloured exfoliative plaques.

Recognition of risk factors that predispose the crusted scabies is often missed or delayed. Furthermore, early identification of severe/crusted scabies cases may be more difficult in patients with reduced self-advocacy for those living with physical and cognitive disabilities. Clinical mimics are common and clinical features and best practice investigations are often implemented late.

25.5 Confirmatory and Supportive Diagnostic Testing (See Detail in Chap. 17)

Supportive and confirmatory diagnostic testing is covered in Chap. 17 but is summarised in the below (Table 25.2):

Techniques described in Chap. 17 for diagnosis such as microscopy of skin scrapings, dermatoscopy, biopsy, ink test and tape stripping are operator dependant and may not be available in all settings [22]. When confirmatory testing is unavailable, diagnosis can be confirmed by examination performed by a clinician with expertise in infectious dermatoses.

Table 25.2 Diagnosis

Confirmatory
Skin scraping
Dermoscopy
Skin biopsy
Supportive
Eosinophilia
Elevated IgE and IgG
Hypoalbuminaemia

25.6 Medical Treatment of the Index Case

25.6.1 Transfer Out to Hospital and Isolate

Severe scabies generally requires inpatient care to ensure effective resolution and also to address the patient's home living area and contacts adequately [6]. If the clinical presentation is mild, the distribution is below a body surface area of 10%, and secondary complications such as infection are not present, the treating team may consider home management. This should only be done in collaboration with specialist infectious disease and dermatological support experienced in management of this condition [18]. These localised and stable cases are not a high proportion of cases of crusted scabies [23].

25.6.2 Workup

For patients being received into hospital, in addition to routine observations and a comprehensive general health assessment, a standardised baseline set of investigations should be completed (Table 25.3). These include diagnostic confirmation,

Table 25.3 Baseline investigations

Baseline weight to guide dosing
Diagnostic confirmation:
Skin scraping for mites, ova, scybala
Health status evaluation
FBE (eos↑, anaemia of chronic disease, leucocytosis/neutrophilia supportive of bacteraemia)
LFT (albumin ↓)
UEC (acute renal impairment +/− electrolyte disturbances)
β-HCG (pre-ivermectin in women of childbearing age)
CRP (often not very high)
Assessment for complications:
Bacterial skin swabs
Blood cultures
Investigation for predisposing factors if not clear at admission:
HIV
HTLV serology
ANA
C3, C4
Immunoglobulins (IgE↑)
T-cell subsets
BSL
Investigation for potential comorbidities:
Strongyloides IgG
Fungal nail clipping (to exclude mimics)
Clinical photography where appropriate
Body surface area assessment

Adapted from International Guidelines [13, 15, 17, 18, 23]

objective evaluation of the health status at admission, assessment for complications and investigation for predisposing factors (if not clear at presentation).

25.7 Assessment of Severity: Grading of Disease Morphology, Distribution and Complications

Treatment duration may be guided by a primary assessment of severity by a novel grading system based on distribution, primary morphology, secondary change and chronicity (Tables 25.4 and 25.5) [23]. While reduction in mortality has not been shown with this stratified approach to systemic treatment, hospitalisation duration was reduced with analogous patient outcomes [23].

Each of the four criteria are scored by the initial clinician, according to mild, moderate or severe, with scoring of 1, 2 and 3 respectively attributed to each of the four categories with a minimum score of 4 and a maximum score of 12.

Grade one: Score 4–6
Discuss if local management appropriate, if not admit to hospital
Systemic treatment day 0, 1, 7 + topical treatments until cure
Grade two: Score 7–9
Admit to hospital
Systemic treatment day 0, 1, 7, 14+ topical treatments until cure
Grade three: Score 10–12
Admit to hospital
Systemic treatment day 0, 1, 7, 14, 21, 28 + topical treatments until cure

Table 25.4 Grading

Body surface area: Mild: <10% Moderate: 10%–30% Severe: >30%	Chronicity Mild: first episode with no clinical evidence of chronicity Moderate: 1–3 prior admissions/localised reactive depigmentation Severe: ≥4 hospitalisations/reactive depigmentation and lichenification/acquired ichthyosis
Primary morphology and depth of hyperkeratosis: Mild: <5 mm depth of scaly debris Moderate: 5–10 mm of scaly debris Severe: >10 mm scaly debris	Secondary changes: Mild: Absent Moderate: Pustulation, impetiginisation, superficial erosion and early fissuring Severe: Widespread deep fissuring with florid purulent discharge

Table 25.5 Policies and procedures for nosocomial outbreaks

OVERARCHING PRINCIPLES
Suspicion for crusted scabies in undifferentiated rashes in patients at risk
Early confirmatory diagnosis
Adequately experienced, trained and resourced multi-disciplinary team to supervise the processes with clearly designated roles and responsibilities
Active surveillance programme for new cases and effective documentation
Vigilant maintenance of a visitor record and staff log to facilitate contact tracing
Coordinated and synchronous treatment where possible
Cessation or reduction of staff rotation to different sites
Clear delineation of roles and responsibilities
Consideration of the need for ward/wing closure, although this might not be necessary
Community activity reduction and social distancing
Funding support for treatment of residents/patients and staff
Adequate stock of oral and topical treatments
Adequate stock of PPE
Adequate staffing levels
Stringent and clear infection control processes including hand-hygiene and PPE use
Robust data collection
Synchronous examination and treatment
Simultaneous treatment for all affected and contact persons
Restriction of unnecessary patient movement in and out of affected facility
Restriction of unnecessary visitors
Minimisation of unnecessary and frequent close patient contact
CASE MANAGEMENT: INDEX CASE AND AFFECTED CONTACTS
Case definition: Index case and affected contacts
Experienced/adequately trained clinicians to perform synchronous examinations in appropriate facilities to diagnose active cases
Regular follow-up examinations
Isolation of index and active cases
Evidence-based treatment protocols for active cases
Treatment of environment, clothing, linen, furniture
Disinfection and decontamination protocols for active cases
Treatment techniques for those who are affected exposures (including written information)
Adequate personal protective equipment (gloves and gown) with hand hygiene on entry and exit of isolation rooms
Restrict staff caring for index and other active cases
Return to work policy (≥24 h after first treatment)
Documented expectations about isolation and treatment prior to returning to work
CONTACT TRACING AND TREATMENT FOR ASYMPTOMATIC CONTACTS
Protocols for contact tracing including staff and social contacts
Protocols and training for recalling and notification of affected contacts
Documented expectations about undergoing prophylactic treatment if asymptomatic
Prophylaxis technique for those who are asymptomatic contacts (including written information)
Prophylaxis for secondary contacts
Prophylaxis for tertiary contacts where appropriate, especially children and partners of staff

(continued)

Table 25.5 (continued)

ENVIRONMENTAL MEASURES
Decontamination of room and fixed objects such as furniture
Daily hot washing of linen, clothing of the index patient and on days of treatment for the affected contacts
Bagged clothed and linen transported to laundry for hot washing
Available replacement clothes and linen
Adequate supply of PPE and cleaning equipment
Universal hand-hygiene ad gloves for cleaning and patient care
COMMUNICATION
Protocols for communicating with staff including regular updates
Protocols for communicating with patients/family members including regular updates
Regular meetings at designated intervals to manage the process
Clear and regular communication with staff, residents/patients and relatives
Appropriately targeted information for those living with disabilities, from diverse backgrounds, have other health issues
Clear documentation of cases and treatments performed
Ongoing education of staff, families and community
Stigma reduction measures
Robust record keeping for population health purposes
Education about participation in prophylactic treatment to reduce failure of the programme and keep tertiary contacts unaffected
SURVEILLANCE AND FOLLOW-UP
Case definition and tracking of treatment failure and reacquisition including reasons
Prolonged and active surveillance phase protocols and staffing to coordinate this
Targeted follow-up of cases and contacts
Monitoring of containment
Regular examination
Monitoring of high-risk contacts for complications
Encouraging reporting of new symptoms
Monitor staff wellbeing and morale
Monitor reputational risk
Early recognition of RF and clinical signs/symptoms
Minimisation of misdiagnosis
Pathway for undifferentiated ‘rash’
Clinical features clearly understood
Low threshold for suspicion
Early notification of cases
Active surveillance programme in high prevalence populations
Contact management summary log
PREVENTION
Targeted education programmes to ensure prolonged latency and atypical presentations are understood
Reporting requirements for new symptoms
Regular review and update of infection control practices

Table 25.5 (continued)

Training about PPE use and hand hygiene with soap and water
Ongoing monitoring of PPE use and hand hygiene practices
Regular reviews of new admissions and transfers
Monitoring of case numbers with plan to reactivate a triage system of identification, isolation and treatment of potentially infected patients and staff
Ongoing review of processes, policies and procedures to optimise standard of care

A: Distribution and extent of crusting

1. Wrists, web spaces, feet only (<10% Total Body Surface Area)
2. Above plus forearms, lower legs, buttocks, trunk or 10-30% TBSA
3. Above plus scalp OR >30% TBSA

B: Crusting / Shedding

1. Mild crusting (<5mm depth of crust), minimal skin shedding
2. Moderate (5-10mm) crusting, moderate skin shedding
3. Severe (>10mm), profuse skin shedding

C: Past Episodes

1. Never had it before
2. 1-3 prior hospitalizations for crusted scabies OR depigmentation of elbows, knees
3. >=4 prior hospitalizations for crusted scabies OR depigmentation as above PLUS legs/back or residual skin thickening / ichthyosis

D: Skin Condition

1. No cracking or pyoderma
2. Multiple pustules and/or weeping sore and/or superficial skin cracking
3. Deep skin cracking with bleeding, widespread purulent exudates

Grade 1: Total score 4-6
Grade 2: Total score 7-9
Grade 3: Total score 10-12

Treatment: Ivermectin 200mcg/kg rounded up to nearest 3mg.
Grade 1: 3 doses - Days 0, 1, 7
Grade 2: 5 doses - Days 0, 1, 7, 8, 14
Grade 3: 7 doses - Days 0, 1, 7, 8, 14, 21, 28

All patients also treated with benzyl benzoate and 5% tea tree oil 2nd daily alternating with Keratolytic cream.

Fig. 25.1 Severity grading scale for crusted scabies. Doi: 10.1371/journal.pntd.0002387.g001

The higher than severity grading, the longer the duration of treatment, extending from a minimum of 7 days in a mild grade one case, 14 days in a moderate grade two case and a full 4 weeks of treatment in severe grade three cases (Fig. 25.1).

25.7.1 Systemic Treatment

Oral ivermectin, augmented by topical therapies (see below), is standard of care for crusted scabies [6, 14, 23, 24]. The medical world's collective awareness of this immunosuppression-related infectious dermatosis as a public health issue re-emerged in the HIV/AIDS epidemic and this medication was repurposed and deemed to be a successful orally ingested systemic treatment for crusted scabies [25–28].

Ivermectin is an avermectin-class anti-helminthic medication that had broad-spectrum anti-parasitic activity against scabies, onchocerciasis and strongyloidiasis [29, 30]. The mechanism of action if by selective binding to the glutamatergic chloride channels in the muscle and nerve cells resulting in elevated cell membrane permeability and hyperpolarisation these cells, causing paralysis and death of the scabies mite [31]. It has in vitro scabicidal efficacy of less than 2 h [32]. While technically an off-label non-FDA-approved use [33], ivermectin is recognised as efficacious and safe and is widely used for crusted scabies, where available. It is best taken with food [13]. It is not readily available in all resource poor and developing communities. Ivermectin has been shown to be safe in infants and children under 15 kg with effective scabicidal properties and infrequent mild adverse events with no serious complications [34]. It is pregnancy category B3; however, case reports of crusted scabies are exceedingly rare, and topical strategies for contacts of index cases are safe and preferred. In most setting it is available as a 3 mg tablet which can be split, rounding the dose up to nearest 1.5 mg.

The dosing regimen for crusted scabies is 200 μg/kg per dose, in three, five or seven standard doses depending on clinical severity [6, 18, 19, 23].

- Mild: Grade One: Day 0, 1, 7.
- Moderate: Grade two: Day 0, 1, 7, 8, 14.
- Severe: Grade three: Day 0, 1, 7, 8, 14, 21, 28.

For treating clinicians and for patients to clearly understand, it is often easier to consider this as *'Monday, Tuesday, Monday, Tuesday, Monday, (Monday, Monday)'* or aligned with whichever day of the week the patient starts treatment. It must be repeatedly re-administered at 7 day intervals for several reasons: ivermectin is not ovicidal and repeat dosing is scabicidal to newly hatched mites [6]; ova hatch into larvae after 2–4 days then develop into adult mites 10–14 days later [35]; mites can survive for up to 7 days in exfoliated hyperkeratotic debris [3], and live mites may easily re-infest from these plate like skin fragments in bed linen and clothing in bedbound unwell people; thickened and hyperkeratotic outer scale is not penetrated by systemic ivermectin and requires keratolytic agents for removal alongside adequate treatment of the skin beneath.

25.7.2 Emerging Treatments

Concerns exist about emerging resistance in rare cases [36, 37] and new alternative systemic treatments are under investigation [38]. Repurposed from veterinary uses in management of animal parasitic infestations, moxidectin has a long half-life,

penetrates hyperkeratotic skin well, is highly lipophilic and has a good safety profile. It holds promise as an effective single dose treatment and clinical trials are underway.

Acitretin has been reported in settings where systemic ivermectin was unavailable and topical therapy failed in two cases of widespread crusted scabies. The beneficial effect was presumed to be increased desquamation of the hyperkeratosis and inhibition of differentiation of keratinocytes [39]. Daily dosing with 30 mg for 8 weeks resulted in clinical and microscopic cure at 13 months.

Methotrexate is of historical note and not used in modern management of crusted scabies to risk of toxicity and more safe and effective alternatives [28, 40].

25.7.3 Topical Therapy

25.7.3.1 Topical Targeted Anti-Parasitic/Scabicidal Agents: An Additional Treatment to Oral Ivermectin

The dosing regimen of oral ivermectin is consistent and standardised internationally and the need for targeted topical scabicidal agents and keratolytic is universally recommended for crusted scabies. While all generally very similar regimens, there are slightly nuanced differences to the targeted topical agents used to augment systemic therapy. Local medication availability, cost, disease patterns and expert preference guide slightly different treatment protocols and regimens. The two most recommended targeted topical scabicidal agents are permethrin 5% cream and benzyl benzoate 25% lotion.

25.7.3.2 Topical Permethrin 5% Cream

Permethrin 5% is a synthetic pyrethroid and potent insecticide. It is considered the most effective topical medication for the treatment of classic/simple scabies [41] and is a useful topical adjunct for crusted scabies. Permethrin disrupts the function of voltage-gated sodium channels of arthropods, causing prolonged depolarisation of nerve-cell membranes and disrupting neurotransmission [20]. The cream should be applied to the entire body including the scalp and face (excluding the perioral and peri-orbital area), overnight or for at least 8 to 14 h, then washed off and the process repeated as per the local protocol [6]. Permethrin is safe drug in children >2 months old and pregnant women.

Occasionally, where oral ivermectin is unavailable, this is used as monotherapy although treatment failure is high [42, 43].

25.7.3.3 Topical Benzyl Benzoate 25% Lotion

Benzyl benzoate is an ester of benzoic acid and benzyl alcohol and is neurotoxic to the scabies mite [44]. It is not expensive and often accessible in resource-poor and developing communities; however, a burning irritant contact dermatitis is common and may limit the use of this [13, 35]. This is second line in the CDC guidelines as it is not readily accessible in the USA [45] and commonly used in Australia. It is a World Health Organisation essential medicine [46].

25.7.4 Other Topical Agents of Note

The use of lindane, an organochlorine insecticide, is contraindicated in patients with crusted scabies due to risk for toxicity and is seldom available outside of resource-poor and developing settings [3, 6]. Extremely localised use has been reported to the nail unit for treatment refractory crusted scabies in the hyponychium [47].

Modified Wilkinson ointment (goudron végétal 12.5%; sulphur 12.5% in petrolatum) for 3 consecutive days, which is known to have both a keratolytic and scabicidal effect [47–51], but is rarely used unless oral ivermectin or topical permethrin is unavailable.

Tea tree oil is a Northern Australian essential oil distilled from the leaves and terminal branches of *Melaleuca alternifolia* of the Myrtaceae family. Tea tree oil 5% added into the benzyl benzoate 25% lotion is advocated for in Australian Guidelines, where available [13, 18]. In addition to augmenting the scabicidal effect of the benzyl benzoate, tea tree oil also has anti-bacterial, anti-inflammatory, anti-pruritic and wound healing properties [38] and may improve the tolerability of the benzyl benzoate which is irritating to the skin. Furthermore, Indigenous people may prefer traditional medicine is used alongside conventional evidence-based medicine for Indigenous populations. New vehicles for tea tree oil are undergoing clinical trials for classic scabies [52], and new/repurposed topical therapies are under investigation; however, these topical agents are unlikely to impact management of crusted scabies where systemic treatment with ivermectin is the current gold standard.

25.7.5 Guidelines: Variations in the Topical Regimen Protocols (in Addition to Systemic Therapy)

American CDC guidelines for crusted scabies recommend application of topical permethrin 5% cream *every 2–3 days* for 1–2 weeks [33].

European Guidelines for crusted scabies [14] recommend either topical scabicide *daily* for 7 days and then twice weekly until cure.

Australian guidelines for crusted scabies [10, 18] advise benzyl benzoate 25% lotion (+/− tea tree oil 5%) *second daily* after bathing for the first week then two to three times weekly until cure is achieved with change to topical permethrin 5% cream if skin irritation develops.

25.8 Removal of Surface Debris

25.8.1 Keratolytic Topical Agents

Hyperkeratotic thick plaques prevent effective topical treatments from penetrating adequately. Keratolytic topical agents are recommended to be used once to twice daily on days when the topical scabicidal treatments are not applied [6, 18]. Options include urea 10% and 5% lactic acid in cream/petrolatum base and salicylic acid 5%–10% in cream/petrolatum base and need to be applied to the whole body [43, 53].

25.8.2 Physical Modalities

Mechanical exfoliation of surface hyperkeratotic debris by soaking and scrubbing is recommended [13, 40, 54] prior to application of targeted topical scabicidal treatments to aid their absorption as well as physical removal of infested scale.

Mechanical debridement may be reserved for extremely thickened and exophytic disabling nodules and plaques, resistant to conventional therapies [55, 56]. Debulking the affected sites may facilitate and intensify the effect of topical scabicidal agents to penetrate and eliminate the mites [56]. Surgical intervention to the affected and most severe areas should only be considered if this is in keeping with the patient's ceiling of care, they are medically fit for the procedure, and sub-acute post-operative rehabilitation care is available.

25.8.2.1 Management of Special Sites

Protected sanctuary sites for mites with high mite burden which need special attention include the anogenital area, umbilicus, scalp and nail units. The anogenital area, umbilicus and scalp require thorough application of both scabicidal and keratolytic topicals with close attention to detail to ensure full coverage.

Nails: The nail unit, particularly the subungual areas, requires adequate and vigilant therapeutic interventions to prevent recurrence. Crusted scabies involving the nail unit can often be refractory to treatment with conventional treatment [47]. There are no standardised treatment protocols for the management of nail involvement in crusted (or simple classic) scabies [57]. Nails should be trimmed short [12] in addition to standard of care treatment with oral ivermectin and topical scabicides and keratolytics. It remains unknown how effectively systemic ivermectin penetrates the keratin of the nail plate [47]. Regular removal of debris as well as generous application of topical anti-scabietic agents and keratolytic is required. However, these subungual sites may be sites of challenging access, particularly when dystrophic onychogryphosis is present and subungual hyperkeratosis abundant. It is a site of relative immune privilege for mites to hide in as a reservoir and a source for relapse/treatment failure [40, 47, 58].

Interventions for nail crusted scabies, are varied and anecdotal. Treatments described rely on therapeutic chemical or procedural [59] onycholysis/nail avulsion with therapeutic topical scabicidal agents applied to the nail bed.

Although contraindicated in crusted scabies for broadly distributed disease due to the risk of systemic toxicity, lindane 1% in petrolatum under occlusion for month has also been used with clinical and microscopic cure [47]. Other reported options have included:

- Urea 40% under occlusive taping [60].
- Salicylic acid 30% [58].
- Phenothrin 5% lotion under occlusion [61].

Randomised control trials are lacking in crusted scabies [62] and treatment regimens are guided by severity and based on expert knowledge and experience. While topical strategies are commonly and effectively implemented in standard scabies as

monotherapy [63], in severe scabies, there is a need for multi-disciplinary and holistic management including addressing complications and associations, using oral ivermectin with additional topical scabicidal and keratolytic preparations and oral ivermectin for severe/crusted scabies with additional frequent topical scabicidal and keratolytic preparations.

25.9 Monitoring of the Index Patient for Complications: Additional Acute Care Requirements

Daily reviews are recommended until cure and safe discharge to a safe and appropriately treated/exterminated facility [13] with regular follow-up plans in place.

Functional impairment of this condition can be profound, often further compounding the underlying disability. Self-care activities are often limited by the primary cutaneous disease process including secondary fissuring changes, pain especially with movement, infectious complications, deterioration of associated predisposing conditions, the need for repeated topical treatments and medical isolation. Impairment of independence is common and often due to physical restriction and pain [64]. This limits activities such as walking, washing and dressing, eating and drinking, and even movement. Baseline functional status should be assessed and monitored against with appropriate multi-disciplinary nursing and allied health care staff involved in team management. Wound care and prevention of pressure injuries associated with prolonged immobility/reduced mobility should be considered as part of this multi-disciplinary approach. Pain management, control of other symptoms, attention to nutrition and hydration/fluid balance status and regular monitoring of routine observations should also be prioritised.

Underlying conditions associated with the development of crusted scabies require assessment and optimisation, where possible. For example, HIV associated crusted scabies requires assessment of both CD4 count and viral load alongside optimisation of anti-retroviral therapy, with standard crusted scabies treatment. Likewise, haematological malignancies, autoimmune disorders, iatrogenic/congenital/acquired immunosuppression, malnutrition, mycobacterial infections such as leprosy and tuberculosis and any other reversible factors should be re-reviewed and improved where possible.

Due to the condition and treatments rendering patients bed bound or reducing their mobility significantly otherwise, if there are no contraindications, deep venous thrombosis prophylaxis is reasonable, adjusted to renal function.

Secondary bacterial, and occasional viral, infection is common and is the leading cause of mortality [17]. Mortality approaches 50% [65] and infection rates are high due to fulminant compromise of the skin barrier function in otherwise immunocompromised people. Although mortality rates have improved following standardised treatment with multi-dose ivermectin, patients require close monitoring and early identification of superimposed infections. This not only facilitates appropriate, targeted and early treatment but allows for close observation. Early empirical broad spectrum antibiotic cover is the standard of care to cover for suspected secondary sepsis [17]. Once an infection is established, suspicion for downstream

complications of the infection, such as infective endocarditis, is heightened and arranging further investigations such as echocardiograms may be expedited. Furthermore, compromised skin barrier with widespread hyperkeratotic plaques and the need for topical treatments may impair peripheral or central venous access for intravenous antibiotics. All of this can take time even in developed countries with universal healthcare and may be challenging and delayed in resource poor settings. Hence, early identification and intervention improves the pathway to adequate and comprehensive care.

Bacterial swabs and blood cultures should be performed with a low threshold in patients with an acute deterioration of pain or haemodynamic compromise. Screening for other common hospital acquired infections including hospital acquired pneumonia, urinary tract infections which may be associated with catheterisation in bedbound patients, and bacteraemia with sepsis which may be complicated by infective endocarditis.

Secondary bacterial infection of compromised and fissured skin is common whereas viral infection is rare. Of patients with severe scabies from a hyperendemic area in Northern Australia, *Staphylococcus aureus* bacteraemia (SAB) was identified in 11% of patients, with a 26% 1-year mortality in those affected [66]. Depending on community resistance patterns, cover for methicillin resistant staphylococcus aureus (MRSA) should be considered while awaiting sensitivities.

Kaposi's varicelliform eruption (KVE) is a rare, superimposed, and often disseminated infection of herpes simplex virus (HSV) atop a simultaneous dermatosis, in this case, crusted scabies [67]. KVE seen in profoundly immunosuppressed people with crusted scabies including poorly controlled HIV/AIDS, haematological malignancies and iatrogenic immunosuppression [67]. An acute onset of painful well-defined vesiculated or ulcerated lesions should raise suspicion. These may be localised, for example to the anogenital area, or disseminated. Clinical suspicion should prompt a confirmatory viral PCR swab for HSV. Empiric treatment should be started without waiting for the result due to the risk of multi-organ dysfunction syndrome and death as a consequence of disseminated infection.

Given mortality can approach 50% [65], there are times when active management described above fails due to underlying comorbidities or sepsis. In such cases, a holistic management may shift to keeping the patients comfortable, understanding their personal and cultural wishes.

In the majority of patients who survive, long-term review and follow-up for reinfection are imperative. This is often best provided by nursing or health workers. Recommendations for early after discharge [14] then at regular intervals between 1 and 4 weekly would be appropriate [13, 40, 68].

25.10 Long-Term Care Considerations of the Affected Patient

After successful treatment of the patient, their environment and their contacts, ongoing surveillance to ensure enduring eradication, monitoring for complications and physical rehabilitation is required. Case management, community support,

psychosocial factors including education about the disease and prevention strategies, and physical disease management including rehabilitation and recurrence prevention are identified as having an important role in many guidelines, particularly in high-risk patients or high-risk settings [13, 35, 68].

In such patients, the following recommendations can be beneficial for the individual and their contacts:

- Formal structured and supportive case management.
- Supportive patient education about the condition and self-management.
- Regular skin examination (1–4 weekly) [68].
- Looking for recurrence of crusted scabies and secondary skin infections.
- Regular application of keratolytic emollient (supplied).
- In some cases, fortnightly benzyl benzoate 25% lotion may be used prophylactically if there are recurrent episodes from inadequate treatment or reacquisition (supplied).
- Monitoring and treatment for contacts (supplied).

A long-term therapeutic case management approach showed benefit in small high-risk Indigenous communities in delivering the above programme of monitoring and provision of topicals [68]. Through targeted active case finding, previously undiagnosed or undermanaged cases of crusted scabies were found, treated and had long-term case management as did the people who were known about who had already been diagnosed and treated. Community engagement, culturally aware and consistent staff, a focus on rapport and long-term education with a focus on self-determination and self-management supported these people and their communities and ultimately lead to reduced number of combined hospitalisations and clinic presentations for scabies and impetigo in contacts [68].

Rehabilitation and management of chronic pain associated with walking, movement and activities of daily living is important, particularly when the disease course has been prolonged, and interventions have been extensive [55].

Cutaneous complications of crusted scabies include dyspigmentation (including depigmentation), chronic skin thickening, alopecia and post-scabietic itch. Depigmentation is chronic and support about the appearance related changes may be needed in some circumstances. Keratolytic emollient is helpful for thickened/lichenified skin and prevents re-infestation. Alopecia outcomes are not studied but are described as non-scarring [69]. Post-scabietic itch can be present although crusted scabies is typically less pruritic than classic/simple scabies. The topical treatment regimen, particularly benzyl benzoate, is often highly irritating to the skin and may be a contributing factor. After satisfying the treating team that the itch is not attributable to persisting or reacquired active infection with clinical examination and microscopic confirmation, management of generalised pruritus involves regular application of a non-irritating soothing moisturiser, patient education about expectations of it lasting a few weeks to short months, and further investigation for underlying internal/systemic causes of generalised pruritus should be undertaken [53]. If there are no contraindications, regular oral anti-histamines may help the symptoms,

empower the patient and facilitate sleep if sedating [7]. Topical steroids can be considered however posing a theoretical risk of further decreasing cutaneous immunity and should be offered in conjunction with discussion with experts in infectious dermatoses, particularly after a targeted history about treatment of contacts and the environmental management to ensure risk of reacquisition is as low as possible.

Psychosocial stigma, misinformation and complex health beliefs are common, and patients often require support and education. Optimisation of environmental primordial factors that contributed to crusted scabies in the vulnerable individual, such as overcrowding and access to health hardware, may also prevent disease recurrence and serious complications in patients with crusted scabies and their contacts [70, 71].

25.11 Management of the Living Space/Community/ Residential Facility

Removing the patient and isolating them allows treatment of the contaminated living area and fomites [28] and reduce passive community spread.

Clothing and linen should be hot washed in 60 °C daily and dried in a hot drier or in the sun [18, 35, 45]. If this is not practical, sealing such items in a plastic bag or strict removal/avoidance from people for at least 7 days [3] in cases of crusted scabies or at least 3 days in classic scabies/contacts of crusted scabies patients.

Ideally, if the patient is from their own home, an examination of the home environment serves two purposes: to assess and treat the contaminated surfaces; and to assess need for ongoing community support including optimisation of living conditions and safety as a discharge location.

Professional fumigation is not required but close attention to detail with vacuuming and safe disposal of infested debris is advised. This should encompass all contaminated surfaces including mattresses and furniture. Where possible, these items should be placed in the sun. Hot mopping and wiping of surfaces is also advised. Some homes and facilities may wish to fumigate but alternatives include pyrethroid sprays, insecticidal powders and insecticide bombs can be considered [18, 53].

25.12 Management of Contacts

Patients with crusted scabies are highly infectious core transmitters [17] of classic scabies [5] with community and nosocomial spread a serious population health issue. Up to half (17%[5]–32%[16]–49%[72]) of healthcare workers (HCWs) involved with care of the index patient may be infected with classic scabies with downstream secondary and tertiary infections in their close contacts commonly seen. Seventy eight per cent of residential care facility roommates of crusted scabies patients can develop simple/classic scabies [72]. Occult presentation of classic scabies in those infected by the index case/core transmitter can be common; thus, it is an important mass prophylactic treatment regimen [5]. Further adding to the

impetus to promptly identify and treat, hospitalised/institutionalised patients' care needs may be deprioritised when there is disruption of managing an outbreak, especially with vulnerable populations [12].

25.13 Treatment of Contacts and Management of Risks: Why It Matters

Treatment of community contacts as well as HCW staff is required to effectively mitigate the risk for a widespread outbreak of scabies. Community contacts including cohabitating relatives including partners and children, close or casual social contacts, sexual contacts, and anyone else that the patient has spent time and contact with should be treated, regardless of symptoms [14]. Likewise, all health care facility members of staff from all parts of the healthcare journey including ancillary staff such as wards people, technical and support staff, allied health, nursing and medical teams all require treatment to prevent transmission to other colleagues and other patients. Mass treatment of all contacts is required due to latency of presentation following a prolonged incubation period after exposure, the frequency of asymptomatic carriers of mites who do not develop symptoms, occult/subtle presentations and difficulty in accessing care and formal diagnosis [12]. Synchronised treatments of all exposed patients, staff and visitors are more likely to lead to resolution of the outbreak [12]. Ideally, where practical, simultaneous scabicidal treatment of all contacts on the same day may lead to improved control [16].

Since its first documented report, outbreaks since 1990 have often relied on topical permethrin 5% [73] as the first line treatment of choice for straightforward exposed contacts [5, 12, 63]. Other topical agents including lindane and other acaricides including crotamiton, benzyl benzoate, sulphur compounds and malathion are used infrequently and only if topical permethrin is unavailable or contraindicated [12]. Lindane is not recommended, particularly in vulnerable populations, due to safety concerns [74] and inferior efficacy [75]. Topical permethrin 5% is efficacious, safe and appropriate for use in children, pregnant people and those with complex medical comorbidities [6, 41, 63, 75]. It can be cost-prohibitive in resource poor locations.

Oral ivermectin has been used for more than 20 years for mass drug administration (MDA) treatment of nosocomial outbreaks safely, effectively, with low risk of minor side effects, and no serious adverse events [7, 76, 77]. Importantly, lessons about safety, tolerability and efficacy have been learned from population health interventions in developing Pacific Island communities. Local protocols and practices will be influenced by the current and emerging evidence of scabies eradication programmes in high prevalence communities at risk. Systemic oral ivermectin MDA programmes are safe and effective in treating both scabies and its complications. The Skin Health Intervention Fiji Trial (SHIFT) implemented separate MDAs in three endemic island communities where classic/simple scabies prevalence was >20% [11]. MDA of a single dose of oral ivermectin was compared against both MDA of a single topical permethrin treatment and standard of care treatment being

active treatment only for those diagnosed with scabies and their contacts. Treatment efficacy at 12 months showed scabies prevalence had declined by 94% in the ivermectin MDA arm; 62% in the permethrin MDA arm and 49% in the standard care arm with reduction in the prevalence of impetigo by 67%, 54% and 32%, respectively [11]. While this is not targeted to crusted scabies or their contacts specifically, evidence of efficacy and tolerability has positive implications for real-world applications of treatment for outbreaks regardless of the reason for infection control strategies. MDA for closed communities such as nursing homes with nosocomial outbreaks should be treated with at least one, preferably two doses separated by 7 days, of oral ivermectin 200 μg/kg, regardless of symptoms, as recommended by the European Guidelines [14].

As with complications of crusted scabies, classic/simple scabies frequently becomes secondarily infected with bacteria, most commonly Group A Streptococcus (GAS) and *Staphylococcus aureus*. Similarly, early identification and empiric targeted treatment of infection in classic/simple scabies associated with contact with a crusted scabies index case may prevent acute and chronic infections and their complications. Acute superficial infections include impetigo/skin sores, cellulitis, abscesses, furunculosis, ecthyma and paronychia. More serious complications include invasive bacteraemia, with *S. aureus* tending to produce infective endocarditis, osteomyelitis and GAS causing necrotising fasciitis. Both can cause multi-organ dysfunction syndrome and death. In vulnerable and typically overcrowded populations affected by GAS, risk of acute post-streptococcal glomerulonephritis (APSGN) and acute rheumatic fever (ARF) is serious and is one of many reasons why aggressive treatment of contacts is enforced [35, 71]. Almost exclusively in resource poor settings, when exposed to a crusted scabies core transmitter, young children commonly acquire simple/classic scabies and are at high risk of secondary infection with GAS which may lead to APSGN or ARF in these young people. Risks of lifelong morbidity and premature mortality are significant [71]. For localised uncomplicated single areas of superficial impetigo in low-risk patients, topical mupirocin may be considered, but is not practical or efficacious in children with broadly distributed lesions at risk of complications [78]. Empiric cover for both GAS and *S. aureus* is recommended with moderate to severe secondary infection of simple/classic scabies and will be guided by local community sensitivity patterns for *S. aureus* (i.e. MRSA or MSSA). In communities with low risk of MRSA and to cover GAS, b-lactam antibiotics (flucloxacillin/dicloxacillin) or a first-generation cephalosporin (cephalexin) is reasonable for 5 to 10 days. Cotrimoxazole is the treatment of choice for regions with high prevalence of MRSA [78]. Intramuscular benzathine penicillin is useful in at-risk populations when adherence may be challenging [78].

A low threshold for consideration and investigation of exposure to an infected crusted scabies core transmitter and examination of household contacts for children presenting with recurrent and impetiginised scabies infections of the skin is ideal although sometimes difficult in practice [68]. Likewise, endemic communities at high risk for complications may warrant targeted monitoring and surveillance for cases of undiagnosed or occult crusted scabies who can be repeatedly re-infecting those around them [68].

25.14 Identification: Outbreak Investigation and Contact Tracing

Epidemics of classic scabies as a consequence of community or occupational close contact with an index case of crusted scabies may last from short months up to several years [12, 16]. This may be more dramatic and challenging particularly if identification of individuals at risk is delayed. Inappropriate choice/modality of treatment of contacts and suboptimal treatment adherence contributes to relapse, treatment failure or re-infestation [16]. Contact tracing for healthcare workers (HCW) may be exponentially more challenging if the patient and/or members of the treating team move between multiple facilities or multiple wards [12, 16, 79]. It is common for healthcare providers to work across multiple locations. Likewise, patients with this condition may endure a delayed journey to access the correct diagnosis and appropriate care which may mean multiple care providers are involved from multiple locations. Multiple linked facilities may be notoriously difficult to contain and direct and indirect costs of containment/management are high [12]. Throughout a typical patient-care journey, hundreds of interactions, some physically distanced and others close-contact, are shared between the core transmitter and nursing staff, multiple medical teams, allied health services and other clinical care providers such as radiology technicians, phlebotomists, essential service providers and students.

Central coordination of contract tracing by experienced clinicians in dermatology, infectious diseases and public health including remote support is critical [5]. To adequately identify and treat contacts, accurate and prompt diagnosis and treatment of the index patient in the first instance is best practice as delayed diagnosis is common and problematic [5, 12].

Contact tracing should be rapid and stringent once a potential case of crusted scabies is suspected or confirmed [12]. Identification of contacts recall for active surveillance, screening and evaluation/examination by trained staff for treatment or prophylaxis would be gold standard [5, 80]. Detailed guidelines for management of crusted scabies and management of epidemic risk and treatment of contacts remain limited [4, 16]. Epidemiological investigation requires case identification of contacts and clear case definition, as well as a standardised pre-emptive and proactive evidence-based treatment protocol. Establishing and monitoring who is an asymptomatic exposure and treating them is important as is isolation and treatment for those experiencing symptoms or demonstrating clinical signs of active disease [7]. Suspicion of clinical scabies should prompt isolation and treatment with return to work permissible 24 h after the completion of the first treatment, with appropriate PPE [7]. Infection control and occupational health should maintain a register of all contacts, active cases, prophylactic treatments completed and any complications.

Contact precautions including long gloves and full-length disposable impermeable protective gowns are recommended [16] in those who are providing direct care to patients with crusted scabies. Those who are under active surveillance and not yet completed their full scabicidal regimen are safe to return to work 24 h after the first treatment; however, universal precautions with gloves and a gown are recommended to prevent potential for transmission to patients.

Likewise, adequate education of early signs and symptoms as well as comprehensive treatment training for those who require presumptive prophylactic treatment for prevention/management of classic scabies is essential. Ongoing surveillance and monitoring is important for new cases who may not have been identified and treated, those who may have failed treatment, cases of reacquisition and complications such as secondary infection, post-scabietic itch and psychosocial distress.

Movement of staff and patients should be restricted when an outbreak is under investigation. New admissions to care facilities for high-risk people, such as aged care facilities and group homes for people living with disabilities, should have a full skin examination including hair and nails as should those returning from hospital stays [7, 77].

When there is risk of a nosocomial outbreak, clear policies and procedures should support containment, including the following key points [5, 7, 12, 68, 77, 81–85].

No new cases for 6 weeks delineate the end of the outbreak [83]; however, this can be exceedingly difficult to achieve. Institutional outbreaks are common and demonstrate the need for clear, detailed and comprehensive evidence-based protocols about prophylactic measures for asymptomatic exposed contacts, treatment of the index case and those they infect, and the most effective strategies and governance surrounding these outbreaks. This is an area of future research opportunity to better guide how communities and facilities consistently manage and prevent outbreaks [7].

25.15 Other Considerations

25.15.1 Economics

The economic impact of multiple medicated treatments for each contact, staff hours worked to treat contacts and performing environmental measures, as well as ward closure and staff members taking time off to adequately treat themselves has been shown to be exceedingly costly, with estimates of more than $40,000 USD and thousands of staff-hours in two separate studies of nosocomial outbreaks related to crusted scabies cases [5, 16]. Investment of time and resources as well as temporary suspension or diversion of routine activities leads to reduced productivity and expense in outbreaks associated with nosocomial infections [5].

Containment and treatment of the index patient/contacts and the environment is high in terms of direct and indirect costs [12, 81]. Direct costs include treatments for all contacts, lost person-hours lost due to sick leave, reduced productivity, ward closures and reduced income, clinician time, redistribution of workplace efforts away from routine activities, cleaning products. Indirect costs include reputational damage, reduced staff productivity due to increased workload and decreased morale, prolonged patient and staff distress from restrictions, and isolation of space and equipment not being used [81].

Direct and indirect economic and time costs of repeated topical treatments for residential and occupational contacts requires a significant investment of staff hours of labour to adequately and thoroughly apply the treatment to those who often live with poor mobility or impaired cognition. Mass institutional treatment with oral ivermectin, as opposed to topicals may be preferable due to convenience, adherence and reduced close contact with patients who need help to apply. Two doses are recommended due to the short half-life and impermeability of the ovum leading to a lack of ovicidal activity [12]. While this is not the most low-cost option in the short term, it must be balanced against ineffective outbreak control and the costs associated with inadequate treatment and a longer period of reduced activity. More expedient control of the outbreak is economically favourable.

Isolation contact precautions are costly for index cases of crusted scabies but helpful in aborting a widespread outbreak. Effectively treating the index case according to the aforementioned grading method allowed for reduction in length of hospital stay (and therefore reduced cost) without increase in relapse or complication rates [23].

25.16 Psychosocial Impact on the Individual and the Community

25.16.1 Cultural Factors Including Stigma and Normalisation

Although stigma and shame around a diagnosis of crusted scabies in an individual or a family may appear at odds with normalisation of skin disease in hyperendemic and endemic communities, both can be synchronous issues that impede effective treatment. In many endemic regions where prevalence of crusted scabies is relatively high and complications are plentiful, HCW and community members paradoxically have normalised skin disease, particularly in children, in the face of competing and complex priorities. Paradoxical normalisation impacts adequate recognition and adequate treatment for those living with high rates of scabies and its complications [86]. In the context of the community impact of crusted scabies, this concerning phenomenon of normalisation of skin disease is most relevant in children who are living with simple/classic scabies and impetigo as a result of contacts with local community core transmitters of this hyper infested variant. This has implications for propagation of serious infectious sequelae including APSGN and ARF [71]. Through community controlled and public health campaigns, an increased awareness in endemic Aboriginal communities is leading to denormalisation of scabies and crusted scabies and improving access to health services and health-seeking behaviours. Local champions, elders, leaders, resources in local languages and cultural broker all play a role in resetting community expectations of child skin health.

Shame and stigma associated with crusted scabies is disabling and limits, delays and prevents help-seeking behaviours. Late or lack of presentation is common. A sensitive, respectful and patient approach can optimise patient connection and improve their access to help. Individual and community stigma is significant which

may impact the speed at which cases are identified as well as adherence to comprehensive treatment strategies for the affected patient and their contacts [10, 35, 70, 87, 88]. This may be more challenging in resource poor environments, culturally and linguistically diverse communities, group homes/long-term care facilities for peoples living with disabilities and residential aged care facilities. For example, Australian Aboriginal remote communities have been recognised as existing with the highest reported incidence in the world documented for crusted scabies, with a 5-year cumulative regional rate of 3 per 1000 [89]. Shame and stigma are well-documented barriers to care in this population, firstly locating these community core-transmitters and engaging in effective chronic disease management [68]. Taking health services to the patients in their community and offering home visits improves access to consistent and coordinated care [68] and may mitigate risks of complications. A chronic disease case management approach, especially around critical times like discharge from hospital, may act as the broker between the complex medical treatment needs and the person who is recuperating. Furthermore, if recurrence leads to readmission, the case-manager familiarising the treating teams with an understanding the needs of the patients and their families, particularly those with complex medical and psychosociocultural needs, can help long-term engagement and improve the patient experience and outcome [90–92].

25.16.2 Organisational Stigma

Likewise, organisational stigma, institutional reputational considerations and staffing may be factors that can contribute to delay in diagnosis or adequacy of treatment in aged or residential care facilities. Negative publicity and malpractice suits have been reported with nosocomial spread of classic scabies related to contact with crusted scabies patients [5].

25.16.3 Anxiety in Contacts

Management of scabies-related anxiety in contacts of a crusted scabies patient [5] requires a robust and clear communication and education strategy. Suggestions for improving outbreak control through communication strategies includes staff in-services training; regular written updates; appropriately targeted factsheets (which may vary between community contacts with limited health literacy as opposed to HCWs); and ongoing educational information [12].

25.16.4 Psychological Complications

Psychological complications [6, 29] can range from disbelief and lack of acceptance through to shame and guilt and may be short lived or chronic. Following a diagnosis of parasitic dermatoses, psychosocial wellbeing and health related quality of life are

negatively overwhelmed: shameful self-perceptions, humiliation, interrupted school or leisure activities, fatigue due to poor sleep and perceived stigmatisation are common experiences [87]. Illness anxiety disorder [93] previously known as monosymptomatic hypochondriacal psychosis or delusions of parasitosis/delusional infestation can follow successful treatment, particularly when the patient is bothered by post-scabietic pruritus [6, 94].

25.16.5 Social Barriers to Care

Disease prevention and treatment as well as maintenance of biopsychosocial wellness can be difficult if access to good housing and social infrastructure like health care and nutrition is limited [90, 92]. Health outcomes may be improved by addressing inadequate access to stable housing, reducing overcrowding, addressing homelessness [89], access to adequate nutrition, communication and literacy infrastructure, personal care and hygiene needs, health hardware, education, employment, clean running water, suitable sanitation, transport and access to services and access to medical care [90, 92]. Sustained improvement of crusted scabies may be challenging without these resources.

Many people who have experienced crusted scabies are able to seek help and articulate their history. However, self-advocacy for people living with advanced physical or cognitive impairments may be extremely limited and often relies on relatives and supportive care-staff to help identify new and emerging skin conditions and seek care. These supports can be inconsistent and may be a reason for delayed diagnosis in these patients.

25.16.6 Further Opportunities

Improved awareness of scabies in general but also notably crusted scabies is essential and may lead to increased suspicion and therefore more prompt diagnosis. Nursing staff, general practitioners and community-based health care providers are more likely to have frequent interactions with the complex patients who are more likely to be afflicted by crusted/severe scabies due to the nature of their chronic underlying health issues. Consideration of the broad differential of pruriginous dermatoses while concurrently managing other health issues is a considerable task for these healthcare providers. However, targeted educational programmes for carers and community care providers may facilitate greater awareness for parasitic infestations. Particularly targeting educational programmes for HCW working with high-risk communities should ideally be supported for improve awareness of infectious dermatoses for example, those providing are for people in residential aged care facilities, group long-term residential care facilities, First Nations populations and people living with immunosuppression. Education on the pathway for accessing help for patients with suspected crusted scabies or advice about an undifferentiated rash is an opportunity to improve speed at which diagnosis is confirmed and

outbreaks contained. This could be expanded to HCW more broadly including education of nurses, community doctors, community health workers and support staff in communicable infectious dermatoses, to minimise missed diagnosis, misdiagnosis and delayed diagnosis. The ultimate goal being implementation of swift and effective treatment for crusted scabies patients and control of outbreak spread of classic scabies and its complications. Early suspicion and swift simple investigations may help identify an index case prior to a widespread institutional or community outbreak [12]. Abundant cases of classic scabies should prompt broad assessment for index cases of crusted/severe scabies locally.

Treatment of this severe, disabling and highly contagious parasitic dermatosis is complex. Admission to hospital and isolation, often to tertiary referral centres far from familiar surroundings, for complex systemic and topical treatment regimens can be overwhelming for the individual and their community. Arising in already immune compromised people, the condition further renders people more immobile and vulnerable due to impaired mobility and the need for frequent bedbound treatments. Through improved and coordinated care, long-term management may lead to fewer complications including recurrence, infection and transmission to contacts. Emerging single-dose therapies may be a piece of this complex puzzle that perhaps may reduce some of the complexity of treatments and improve cure rates.

The breadth and severity of the burden of crusted scabies is poorly understood internationally. Ongoing surveillance programmes, patient registers and population studies, particularly in endemic communities, to better quantify the issue may lead to improvements in our understanding of this condition and highlight further research questions. Improved research resources for this neglected tropical disease may lead to improved insights into pathophysiology, best practice management of crusted scabies and complications, and long-term prevention [68].

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Management of Pediatric Scabies

26

Aurélie Morand and Stéphanie Mallet

26.1 Overview

There are currently no specific protocols for the management of scabies in young children under 15 kg (under 5 years old). Many cures used to treat adult scabies are not authorized for use in children or even can be contraindicated. This chapter aims to provide guidelines to the management of scabies in children under 15 kg along with a summary of the efficacy and safety of antiscabies treatments in this population. In older children, the management could be similar to adults, and this topic won't be covered here [1].

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The expected outcomes of the treatment are:

- Cure
- Toleration
- Limited complications
- Limited contagiousness
- Improved life quality

Test treatment should be avoided as much as possible. In fact, in the event of persistent pruritus or some persistent nonspecific dermal lesions, the diagnosis can be more difficult (treatment failure, recurrence, postscabious pruritus, or other dermatosis). When scabies is not confirmed, convincing parents and contact subjects can be challenging. Finally, treatments can have adverse events, especially in young children [2–5]. Even though scabies diagnosis is clinical, complicated cases should be referred to specialists before treatment's initiation. The healthcare workers are supposed to have the means of performing correct diagnosis by demonstrating living *Sarcoptes* during the parasitological examination and/or thanks to the use of the dermatoscope [6]. The use of polymerase chain reaction (PCR) molecular analysis can be an added value [7]. And yet, the negativity of the tests (parasitological examination, dermatoscope, and PCR) does not rule out the diagnosis.

26.2 Drugs Available

The drugs used in children are the same as in adults [1]: topical permethrin 5%, topical benzyl benzoate 10%/25%, ivermectin (oral or topical), topical crotamiton 10%, topical sulfur 5%–10%, topical lindane 1%, topical esdepallethrin 0.63% (currently withdrawn from the market), and topical malathion 0.5% (currently unavailable in this indication).

However, ongoing therapeutics protocols used to treat children lack pediatric drug formulation. Additionally, the various treatment decisions are age dependent, especially in child under 15 kg (weight below which the central nervous system is still very immature). In particular, the P-glycoprotein located on the apical face of the endothelial cells of the blood–brain barrier, encoded by the MDR1 gene, is in lower quantity in very young children, and few studies have evaluated the tolerance of oral ivermectin in this population [8, 9].

In children, like in adult population, both topical and systemic antiparasitic treatments should be given in two doses [10].

Topical treatment should be chosen as first attempt. Topical permethrin is well known, and data of safety and efficacy are high in children older than 2 months old [11]. Benzyl benzoate is also well known as safe and effective in children older than 1 month old [12]. Topical sulfur ointment is commonly used and safe in children, although its odor and messy application can compromise adherence to treatment

[13]. Oral ivermectin is now also being used in children, even under 15 kg [14–19] who represent the age group under whom there is no use authorization. The oral ivermectin can be proposed as a second choice when local treatment fails (recontamination, inappropriate application). Scabies can often affect extremities, head (face included), hands, and feet in the pediatric population (25% of infants) [20], implicating the use of the topical treatment in these areas with a risk of eye and mouth contact and ingestion. Under these circumstances, hand's bandages can be used or oral ivermectin can be an alternative treatment.

We recommend the following treatments and dosages in children:

- Topical permethrin 5%, application 8 h on the whole skin (head and face, finger, toes, armpits, and genital area included, avoid mouth and eyes and all mucus membranes of the body) 15 g in children from 6 to 12 years old, 4 hazelnuts; 7.5 g in 1 to 5 years old children, which is equivalent to the size of 2 hazelnuts; 3.75 g in 2 months to 1 year old children, which is equivalent to the size of one hazelnut (The quantity can be increased according to the corpulence of the child in order to cover the whole body).
- Topical benzyl benzoate 25% should be diluted with water to obtain a 12.5% solution when used in 2- to 12-year-old children (1 mL water for 1 mL product) and 6.25% solution when used in 1 -month to 2-year-old children (3 mL water for 1 mL product). The final product should be applicated and kept 24 h on the whole skin (head included) in children older than 2 years old; and let 12 h in 6-month to 2-year-old children and 6 h in 1-month to 6-month-old children. A 10% topical benzyl benzoate exists in some country and could be used in children older than 2 years old but should be diluted (1 mL water for 1 mL solution) for children from 1 month to 2 years old.
- Sulfur 5%–10% is safe in children, even those younger than 2 months old, and could be used as a 2% preparation ointment for the young children. Put the ointment on the whole skin each night for three nights and repeat this protocol after 7 days. Do not cover treated skin with a bandage except for the infants' hands. Heat or bandaging can increase the amount of drug absorbed through your skin and may cause harmful effects.
- Oral ivermectin 200 μg/kg/day at day 1 and day 10. A pharmaceutical preparation should be proposed when possible. In case it would be complicated to have pharmaceutical preparation experts admit the use of 3mg oral tablet cut in ¼ or ½ (depending on the weight) and crush in water or apple sauce. This medication should be given during a meal for better absorption.

Table 26.1 shows the different recommendations available for children under 15 kg. Treatment's availability depends on the residence country.

Figure 26.1 details the algorithm for the management of scabies in children under 15 kg.

Table 26.1 Different recommendations available for children under 15 kg depending on the residence country

Recommendations in children under 15 kg	Oral ivermectin	Topical permethrin 5%	Topical benzyl benzoate 10%	Topical malathion 0,5%	Topical crotamiton 10%	Topical lindane 1%	Topical sulfur 5–10%	Topical esdepallethrin 0,63%	Topical ivermectin 1%
WHO[a]	Safety of ivermectin in pregnant women or children under 15 kg body weight has not been established	Allowed	Allowed	Not discussed	Not discussed	Not discussed	Allowed	Not discussed	Not discussed
Marketing authorization in the French public drug database[b]	Contraindication under 5 years Can be used in breastfeeding women, if necessary	Possible after the age of 2 months (2 applications D0 and D8, exposure time between 8–12 h, amount of cream depending on age) Can be used in breastfeeding women, if necessary	Possible after the age of 1 month, (2 applications D0 and D8, 1 single whitewash before the age of 2 years, 2 whitewashes at 15 min intervals after the age of 2 years, exposure time < 12 h in children under 2 years old, or even 6 h in very young children) Can be used in breastfeeding women, if necessary	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed

French reference center of teratogenic drugs[c]	Can be used in breastfeeding women, if necessary, by weighing the benefit risk balance. No adverse event has been identified	Can be used in breastfeeding women, if necessary, by weighing the benefit risk balance. No adverse event has been identified	Can be used in breastfeeding women, if necessary, by weighing the benefit risk balance. No adverse event has been identified	Possible during breastfeeding by suspending breastfeeding for the duration of the application (8 h)	Not discussed	Not discussed	Not discussed	Not discussed	In front of significant systemic passage, we prefer to use other molecules in a breastfeeding woman
USA (CDC[d]*, American Academy of Dermatology Association*[e]*)*	To be considered as second intention, not validated in children under 15 kg	Possible after the age of 2 months	To be considered as second intention, 10% concentration	Not discussed	Not recommended for children	To be considered as a second line, should not be used in premature children, should not be used in children with very irritated skin Must not be used in pregnant/ breastfeeding women	No danger in children even less than 1-month-old	Not discussed	Not discussed

(continued)

Table 26.1 (continued)

Recommendations in children under 15 kg	Oral ivermectin	Topical permethrin 5%	Topical benzyl benzoate 10%	Topical malathion 0,5%	Topical crotamiton 10%	Topical lindane 1%	Topical sulfur 5–10%	Topical esdepallethrin 0,63%	Topical ivermectin 1%
UK (Medinfo[f], British Association of Sexual Health and HIV[g], British association of dermatologists[h])	Not recommended for children under 15 kg Probably compatible with breastfeeding	Not discussed in children Authorized in breastfeeding women, but breastfeeding must be suspended during application and resumed only after rinsing	Authorized in children and infants, diluted two or three times	Not discussed in children Authorized breastfeeding women, but breastfeeding must be suspended during application and resumed only after rinsing	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Canada (Canadian Paediatric Society[i])	Safety non established under 15 kg and in breastfeeding women	Allowed for children older than 3-month-old	Allowed for children, 10–12.5% solution	Not discussed	Not discussed	Caution in young children, apply 6-8 h	Safety data available in young children	Not discussed	Not discussed
China medical university hospital[j]	Not discussed	Indicated in children (age not specified)	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed

[a] https://www.who.int/news-room/fact-sheets/detail/scabies
[b] https://base-donnees-publique.medicaments.gouv.fr/
[c] https://www.lecrat.fr/
[d] https://www.cdc.gov/parasites/scabies/health_professionals/meds.html
[e] https://www.aad.org/public/diseases/a-z/scabies-treatment
[f] http://www.medinfo.co.uk/conditions/scabies.html
[g] https://www.bashhguidelines.org/media/1137/scabies-2016.pdf
[h] https://www.bad.org.uk/shared/get-file.ashx?id=127&itemtype=document
[i] https://www.cps.ca/en/documents/position/scabies#Table1
[j] https://cmuh.org.tw/HealthEdus/Detail_EN?no=7143

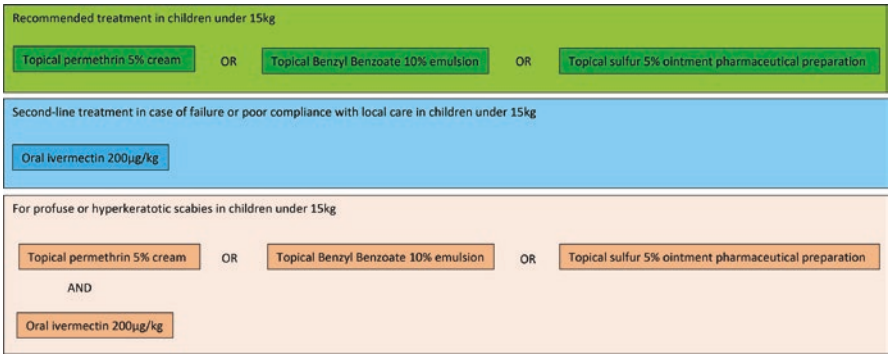

Fig. 26.1 Algorithm for the management of scabies in children under 15 kg

26.3 Failures/Complications

Failure of the treatment is common in children, requiring a repetition of the adapted protocol for a complete cure.

Moreover, especially in children because they have tendency to scratch involuntary, the clinical presentation can change the management and thus the treatment can become more complicated [20]:

- In case of impetiginization [21], oral antibiotic therapy (usually amoxicillin and clavulanic acid, 80 mg/10 mg/kg/day) should be quickly introduced.
- In the event of eczematization, emollients and even local steroids could be useful.
- If the skin is too damaged, using oral ivermectin would be better than topical treatments that would be less tolerated.
- For profuse or hyperkeratotic scabies, patients should be referred to a specialist. There is no consensus in those specific cases, but combining oral, topical treatments and drastic environmental measures seems relevant.
- Itching can persist from few days to weeks after treatment even in absence of treatment failure. Emollient can be used in such cases.
- Altered quality of life, school absenteeism, and stigmatization could occur. Scabies are among the dermatological conditions having a heavy impact in the pediatric population, and psychological care should be proposed.

26.4 Particularities of Newborn and Breastfeeding Women

Regarding the drugs available for children, breastfeeding women of children older than 1 month old should be easily treated with topical permethrin, topical benzyl benzoate, or oral ivermectin. But newborns, premature babies, and breastfeeding women of newborns under 1 month old and of premature babies should be referred to a specialist, and treatment should be decided based on the context. Most of the

time, treatment should not be proposed without diagnostic confirmation. And the treatment should result in the administration of topical permethrin or benzyl benzoate, diluted and let on the skin during a reduced time with bandages on the hands to limit ingestion.

26.5 Contact Cases, Communities, and Outbreaks

The treatment of contact cases depends on the context (common scabies: first circle = parents, siblings; profuse scabies: second +/− third circle; outbreak: second +/− third circle).

The management of contact cases of pediatric index case must be adapted to each situation according to the age and type of care of the child: nursery, childcare, nanny, family, etc. Concerning the other children and the caregivers in childcare, nursery, nanny, etc., there is no consensus. No systematic treatment Is recommended for the other children and adult caregivers who were in contact with a single case of scabies in the community. When several pediatric scabies cases occur, children and adults of the community should be referred to a specialist. The child should be treated in case he/she is in a cluster of scabies even if there is no consensus [22–25]. An eviction from the community up to 3 days after treatment can be discussed based on the situation but usually the children can go back to the collectivity the day that follows treatment's initiation [23]. Scabies is not reportable as a communicable disease, unless associated with an outbreak [23].

26.6 Environment

In young children, priority should be given to physical measures for environmental decontamination [3, 26, 27]. Suction, freezing, machine washing at 60 °C, and storage up to 3 days (scabies mites do not survive more than 2–3 days away from human skin) [23] can be used to avoid the use of spray-type insecticide A-PAR which might be toxic [3]. Those measures should include the decontamination of the pacifiers, loveys, security blankets, car seat, play mat, etc.

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Drug Resistance

27

Kate E. Mounsey, Robert J. Harvey, and Bart J. Currie

27.1 Introduction

When used correctly, the main treatments utilised for scabies appear to remain effective. Recent systematic reviews have found that at four-week follow-up, the clearance rate for one to three doses of topical permethrin was 93%, and for one to three doses of oral ivermectin, it was 86% [1]. Despite this high efficacy in controlled trials, the real-world experience of scabies treatment paints a different picture. Successful treatment of scabies is frequently hampered by application errors, inconsistent treatment of close contacts and uncertainties regarding the importance of environmental decontamination. Furthermore, the pharmacokinetic properties of most current scabies drugs are inherently incompatible with the *Sarcoptes scabiei* life cycle, meaning that single-dose regimens are more likely to fail. Consequently, assessing the relative contribution of mite drug resistance to scabies treatment failure is a challenging task. In this chapter, we will summarise current understanding of drug resistance in *S. scabiei* by assessment of clinical reports, laboratory evidence and molecular data. We will discuss historical observations with drugs now used less conventionally, but mainly focus on Permethrin and Ivermectin, which are of key relevance.

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27.2 Clinical and Laboratory Evidence of Drug Resistance in Scabies Mites

Due to the aforementioned difficulties in assessing treatment failures, equivocal demonstration of mite drug resistance remains limited to a few case reports and laboratory studies. He we summarise the literature for the three most commonly used treatments for scabies in developed countries over the past 20 years: Lindane, Permethrin and Ivermectin.

27.2.1 Lindane

Lindane (gamma-hexachlorocyclohexane) is an organochlorine insecticide that targets both mammalian and arthropod gamma-aminobutyric acid (GABA)-gated chloride channels. Due to neurotoxicity and environmental concerns, lindane is no longer widely used, but it remains as a second line treatment for scabies in some regions of the United States. Lindane has been banned in agricultural settings and is a declared human carcinogen [2]. There are several convincing reports of lindane resistance in institutional outbreaks when the drug was still used in the 1980s and 1990s. While some of these studies are difficult to interpret due to the utilisation of combination treatment strategies, in most, scabies persisted even when mass treatment and environmental decontamination was employed. Yonkosky [3] reports lindane treatment failure in three separate facilities, despite multiple applications and treatment of all asymptomatic patients and contacts. In these cases, the outbreaks were resolved using 5% permethrin, which at the time was only available for compassionate use. Purvis [4] notes lindane resistance in a hospitalised patient with crusted scabies which spread to contacts, who were also not responsive to lindane. There are several other reports where lindane treatment failure could not be attributed to incorrect acaricide application [5–9]. A very large institutional outbreak in Switzerland failed to respond to control with lindane [10], although not all asymptomatic contacts were initially treated.

While the above reports show good evidence of the existence of lindane-resistant *S. scabiei*, there have been only two studies of mite sensitivity to lindane *in vitro*, undertaken on crusted scabies patients from northern Australia. A 1994 publication describe smites still alive after 6 h of lindane exposure [11], but in 2000, Walton and colleagues [12] showed *in vitro* lindane toxicity within 3 h. This suggests that lindane resistance may have been limited to isolated cases or was reversed with the increasing use of Permethrin in this region from the mid-1990s.

27.2.2 Permethrin

The only definitive demonstration of permethrin resistance to date comes from a population of *Sarcoptes scabiei* var. *canis* mites maintained on an experimental rabbit model. A lack of clinical response to permethrin was observed after years of

using the drug to limit the spread of infestation on the host skin, with *in vitro* testing showing a median survival time of 15 h. In comparison, *S. scabiei* var. *suis* mites from a drug-naïve porcine model had a median survival time of 4 h [13]. Similarly, *S. scabiei* var. *suis* mites from a porcine model in France had a median survival time of 2 h upon exposure to 4% permethrin spray [14]. There have been several *in vitro* studies undertaken on *S. scabiei* var. *hominis* mites collected from northern Australia, where permethrin has been used widely since the mid-1990s. The results suggest that while resistance cannot be confirmed, there is a trend for increasing tolerance, with *in vitro* survival times positioned between permethrin naïve and permethrin-resistant populations (Table 27.1). Initial studies by Fraser [11] noted a survival time of 1 h. Only 5 years later, the slow *in vitro* activity of permethrin was noted with 35% of mites alive after 3 h of exposure, and 4% still alive after overnight exposure [12]. A follow-up study in 2004 reported a median survival time in this population of 8 h [15], and in 2008, the median survival time was 6 h [16]. From this, it appears that permethrin resistance may be emerging in *S. scabiei* var. *hominis* populations under ongoing selection pressure from frequent use in remote communities. It is difficult to compare all of these results directly due to the use of different host-derived variants of *S. scabiei;* however, genetic analysis undertaken to date suggests that the permethrin drug target (sodium ion channels encoded by the *Vssc* gene) shows strong genetic identity [17] between the different host variants. Another consideration is that while for most part, the above studies used consistent

Table 27.1 *In vitro* studies of permethrin sensitivity in *Sarcoptes scabiei*

Mite population, origin and year	Median survival time (hours)	Drug exposure history	Reference
S. scabiei var. *hominis,* Australia, ca. 1994	1	Prior to permethrin introduction	[11]
S. scabiei var. *hominis,* 1997–1998, Australia	>3 h[a]		[12]
S. scabiei var. *hominis,* Australia, ca. 2004	8		[15]
S. scabiei var. hominis, Australia, 2008	6	Patient with previous history of IVM resistance	[16]
S. scabiei var. *suis,* Australia, 2008	4	Experimental model with no acaricide exposure history	[13]
S. scabiei var. *suis,* France, 2015	2	Experimental model, no acaricide exposure history. Four per cent permethrin spray	[14]
S. scabiei var. *canis,* USA, 2008	15	Experimental model, clinical failure observed	[13]

[a]Median survival not directly reported, value obtained from interpolation of survival curve presented, 35% mites remained alive after 3 h, 4% alive after overnight exposure

methodology, there may be some differences in active formulation and excipients in the commercial products assessed. It is also recently noted that there are mite developmental differences in sensitivity, with Mounsey et al. [18] reporting that nymphs and larvae have shorter survival times than female mites in response to macrocyclic lactones. As the numbers of relative life stages used in *in vitro* studies were often not reported, it is difficult to assess the potential contribution of this to results obtained.

Definition of a true drug-resistant *S. scabiei* phenotype is difficult, since mites cannot be cultured, and widespread *in vitro* studies are not routinely possible due to difficulties in obtaining sufficient live mites. It has however been observed that motile mites could still be isolated 12-h post permethrin treatment from patients in Germany, where concerns of permethrin resistance are mounting [19].

No data exist for other regions globally, but it is of considerable interest that the incidence of scabies appears to be increasing during the past decade, especially in parts of Europe and the United Kingdom. Anecdotal reports of treatment failure are increasing among practitioners, leading to efforts to better understand whether this is due to permethrin resistance or other factors. As first line treatments can differ even between closely located countries, the following studies provide some useful insights into trends of treatment uptake and efficacy in recent years.

Initial randomised controlled trials undertaken in Germany when permethrin was first introduced (2004) showed an efficacy >90% with single-dose treatment [20], in concordance with other findings [1]. Interestingly, this study included regional stratification, as the neighbouring Netherlands had been utilising permethrin for a decade earlier and the authors wanted to determine whether potential mite resistance influenced treatment efficacy. No significant differences between regions were observed. These findings contrast with more recent observations in Austria and Germany where reduced efficacy is now observed.

In a 2019 review, Sunderkötter and colleagues [19] attempt to dissect causes for treatment failure in Germany, where permethrin has been used for around 20 years. Scabies is not a notifiable disease, but the number of patients receiving treatments for scabies has increased by as much as 200% in some regions. The authors suggest that this value may be inflated by increased awareness of the disease among practitioners, and a high potential of false-positive reports in clinical diagnosis, but nonetheless concluded a true increase in incidence was likely. More solid evidence comes from an increase in inpatient diagnosis, where patients are assessed by dermatologists and the presence of scabies can be confirmed by microscopy and/or dermoscopy. There have been several examples where live mites have been identified despite multiple repeat applications of permethrin, normally be expected to be >90% effective. From this, the authors remarked that ‘patients do not respond to treatment with permethrin as quickly today as they used to some years ago’ [19].

Like the above studies on inpatients, an interesting report on the German Armed forces (Bundeswehr) provides strong evidence due its emphasis on microscopy or dermoscopy confirmed diagnosis [21]. This retrospective clinical review from 2012 to 2019 revealed a three-fold increase in scabies prevalence, as well as an increase in treatment refractory cases. This is insightful, because ‘treatment failure’ and subsequent inpatient admission for treatment was only defined after three cycles of permethrin treatments. While most treatment failures were attributed to reinfection

from untreated contacts 8.7% of cases were deemed 'treatment resistant'. A mail-in survey of General Practitioners across Germany investigated perceptions of topical permethrin treatment efficacy. Efficacy was rated as 'good to very good' in 74% of respondents. Where treatment failures were reported, 62.4% attributed this to application and compliance issues, whereas a substantial proportion (18.8%) suspected the development of mite resistance [22].

Similar to the above experience in Germany, clinics in Norway also report a recent increase in scabies diagnoses. Although scabies is not a notifiable disease, mite infestations may be reported on Norwegian disease outbreak and syndromic surveillance systems. Examination of clinical reports and prescribing data showed a three-fold increase in scabies treatment sales and consultations in the period 2013–2018 [23]. In Norway, permethrin is the first line treatment, with ivermectin only used in severe cases or in the case of treatment failure. The sales of both drugs increased in Norway from 2014 to 2018. Of ivermectin prescriptions, 6.7% were attributed in the system as 'unsuccessful use of permethrin' [23]. From this data it is not possible to determine whether this lack of success was due to inadequate application, re-infestation from untreated contacts or mite resistance.

An Austrian trial investigated the efficacy of topical permethrin, and specifically whether more intensive application would improve treatment outcomes [24]. All patients had diagnosis confirmed via dermoscopy. While one group received standard treatment (n = 42, two applications 1 week apart), the other group (n = 13) received standard treatment in addition to daily application of permethrin at dermoscopy identified sites of infestation. Only symptomatic contacts were treated. Patients were followed up at 2–3 weeks, and again at 5 weeks post-treatment. In both treatment groups, efficacy was only 31% at the first follow-up as confirmed by dermoscopy, with mites reduced in number but still present. While the study had some limitations in the treatment of contacts and a lack of supervised treatment, the multiple applications and timing of follow-up suggest that the observed poor efficacy may indeed relate to the presence of permethrin resistance in this population.

27.2.3 Ivermectin

Oral ivermectin has been increasingly utilised for scabies over the past 20 years. It was originally used off-label to support outbreaks in institutional settings where topical treatment was not effective [25], and in the treatment of crusted scabies, which can be difficult to treat topically. The first report of clinical and *in vitro* ivermectin resistance was in 2000, from two crusted scabies patients who had received multiple doses of ivermectin over many years for recurrent crusted scabies. These patients did not respond to oral ivermectin even after multiple doses, with live mites observed 26 days post commencement of treatment. With large numbers of mites obtainable from these patients, *in vitro* studies were possible and revealed that mites survived after overnight exposure to the drug, where the median *in vitro* survival time was conventionally less than 2 h. These ivermectin-resistant cases were

subsequently resolved by incorporation of topical 25% benzyl benzoate supplemented with 5% tea tree oil, with intensive keratolytic therapy [26].

A later study done on an expanded cohort of crusted scabies patients in northern Australia, showed that median *in vitro* survival times to ivermectin had consistently and significantly increased, doubling from 1997 to 2006. This result was maintained even when the two specific cases from 2000 were excluded from the analysis, suggesting that changes are occurring more widely in the community. Furthermore, a study undertaken in a single patient who received three ivermectin doses within 8 days showed significantly increased survival times at Day 8 relative to Days 0, 3 and 6. While these mites were not defined as resistant, the clear change in survival times shows that if ivermectin is used as monotherapy in crusted scabies selection for resistant populations of mites could rapidly occur [27]. Additional laboratory studies confirmed biochemical and molecular differences in these selected 'tolerant' populations of mites (detailed below) [16].

Another report of ivermectin resistance in crusted scabies comes from Fujimoto and colleagues [28]. In Japan, ivermectin has been licenced as a first line treatment for scabies since 2006. In this case, crusted scabies persisted despite 6 doses of ivermectin. Initial errors with weight estimation meant that initial doses may have been sub-therapeutic, which likely selected for treatment tolerant mites and eventual resistance. The patient was then treated with topical lindane, benzyl benzoate and crotamiton to resolve infestation. A second report of probable ivermectin resistance in Japan was from 2010, in two dogs with sarcoptic mange [29]. These dogs did not respond to multiple doses of 300 μg/kg ivermectin. The first treatment was administered orally. Worsening lesions were observed 14 days post treatment, when a second oral dose was given. The dogs then received a third dose subcutaneously at Day 28, with live mites still observed at Day 35. The infestations were subsequently cleared with 3 doses of fipronil, administered at 2-weekly intervals. Although no *in vitro* studies were done to confirm resistance, this case of treatment failure was likely to represent genuine ivermectin resistance, given that multiple doses and different administration methods were employed, and that two different dogs from the same household were affected.

Although ivermectin has been used with great success for mass treatment in institutional outbreaks such as aged care facilities, scattered reports of treatment failure still exist. In an Amsterdam nursing home in 2007–2008, treatment with topical lindane plus two doses of oral ivermectin failed to resolve the outbreak, with treatment switched to 5% permethrin [30]. Asymptomatic contacts treated with ivermectin prophylactically still developed scabies – this is not surprising given the short half-life of the drug, meaning that longer-term protection is not afforded. While ivermectin resistance was presumed by the authors, it is difficult to gauge this due to asynchronous mass treatment and theoretical potential for re-infestation. Nofal et al. [31] showed variable responses to ivermectin in crusted scabies in a study of eight patients with varying degrees of clinical severity. Crust thickness was positively associated with the number of doses required to clear infestations, showing that ivermectin may not adequately penetrate hyperkeratotic crusts, which is exacerbated by its short half-life in plasma. This further demonstrates the need for combined topical and keratolytic therapy, not only to achieve clinical resolution, but

to prevent suboptimal drug concentrations selecting for resistant mites. Another valid point raised by the authors was that decreased sebum production in dry, elderly skin, may impair delivery of the highly lipophilic ivermectin to the stratum corneum. This has been confirmed by Haas [32], who confirmed decreased levels of surface ivermectin in drier areas of skin. As mites reside in the stratum corneum, and immature stages of *S. scabiei* can be present on the skin surface, this issue deserves more attention.

Ivermectin has been licenced as a first line scabies treatment in France since 2001. Like other western European countries, there has been a noticeable increase in reports of scabies in recent years (where the disease is notifiable) and concomitant increase in sales for ivermectin and benzyl benzoate. An observational study attempted to identify factors associated with therapeutic failure in 31 scabies patients [33]. In this cohort, ivermectin was the most commonly prescribed treatment (84%). While the majority of patients reported undertaking decontamination activities, only 58% of contacts were treated despite over 80% receiving advice regarding the importance of this. The authors concluded that insufficient treatment of contacts was the most likely reason for poor therapeutic response, as well as the absence of a second treatment to eradicate mites from newly hatched eggs (only 65% received two doses). While clinical resistance could not be confirmed in this study, it was notable that 35% of patients had treatment failure despite taking two doses of ivermectin, decontamination and treatment of contacts. Another French observational study on a larger cohort of patients found similar results, with approximately 30% not responding to treatment [34]. Multivariate analysis showed that treatment failure was associated with only using one dose of ivermectin (OR 6.62, $p < 0.0001$). Interestingly, a lack of decontamination of fomites increased risk of treatment failure (OR 5.81, $p = 0.0014$) as did inadequate treatment of contacts (OR 2.13, $p = 0.03$). The treatment of fomites is not usually emphasised as necessary in cases of ordinary scabies, so this finding was interesting and suggests more research should be done on the role of fomites in scabies transmission.

The above reports which suggest that *Sarcoptes scabiei* may be showing signs of developing of ivermectin resistance are in contrast to some other large clinical trials of Mass Drug Administration (MDA), which show sustained success with ivermectin, even when used as a single dose. However, it should be emphasised that these trials utilised a second dose of ivermectin if scabies was clinically diagnosed [35, 36]. Other single-dose MDAs with ivermectin were less successful [37], although the populations differed significantly in terms of inter-community mobility and potential influence of core-transmitter crusted scabies patients. A new study is planned to evaluate one versus two doses of ivermectin in the MDA setting [38].

27.3 Permethrin and Ivermectin Resistance in Other Parasites

While there is strong suspicion and some clear clinical and laboratory evidence for emerging drug resistance in *S. scabiei,* definitive reports remain isolated. It is useful to briefly review on the situation in other parasites of medical and veterinary

importance, where insecticide and acaricide use can be widespread, intensive and indiscriminate, to predict what may occur in scabies.

Resistance to pyrethroid insecticides is common and includes a wide spectrum including head lice, bed bugs, ticks, cockroaches and mosquito vectors for malaria. In head lice, the declining effectiveness of pyrethroids has been recognised since they first became available in the 1980s. Clinical trial data from the United States show that the efficacy of permethrin has declined consistently over the past 35 years and is now as low as 25% [39]. Efficacy is similarly low in the United Kingdom, and resistance appears to be global, although significant regional variation exists [40]. Pyrethroid resistance is also reported in bed bugs (*Cimex lectularius),* especially with the use of insecticide treated bed nets [41]. Elsewhere, permethrin-resistant bed bugs have been reported in Europe [42], the United Kingdom and Australia (reviewed in Dang et al.) [43].

In the acari, where comparisons to *Sarcoptes* are more relevant*,* permethrin resistance is common in the brown dog tick (*Rhipicephalus sanguineus*) and cattle tick (*R. microplus)* [44]. Global surveys have demonstrated foci of permethrin resistance in Florida and the Caribbean with 90% to 100% of *R. sanguineus* having a resistance genotype (determined from sodium channel gene mutations). Conversely, ticks in Africa, Asia, Europe and Mexico possessed a permethrin-sensitive genotype [45]. The poultry mites, *Dermanyssus gallinae* (poultry red mite) and *Ornithonyssus sylviarum* (Northern fowl mite) are highly permethrin resistant in Europe and the United States [46–48]. A recent study on *O. sylviarum* showed that resistance has persisted in these populations even though the drug has not been used in over a decade, suggesting that permethrin resistance is not reversible [49].

Ivermectin resistance was initially reported in the nematode *Haemonchus contortus,* only 3 years after the drug was introduced [50]. Since then, resistance has evolved in many other nematode parasites of veterinary significance including *Dirofilaria immitis* (heartworm) [51]. However, until recently, it had not been a major concern for treatment in humans. The drug has been approved for over 35 years for the treatment of *Onchocerca volvulus* and has revolutionised the control of onchocerciasis in Sub-Saharan Africa. While still largely effective, suboptimal responses are reported in some areas, such as Cameroon and Ghana. In these regions it appears that while microfilariae are still susceptible to ivermectin, the prolonged effect on adult fecundity is not as pronounced which limits success of control [52, 53]. In comparison, moxidectin appears to suppress fecundity for longer duration and has now been registered for the treatment of onchocerciasis [54].

Psoroptes ovis is the non-burrowing ectoparasitic mite causing Psoroptic mange in sheep and cattle. There are many clinical and biological similarities with scabies, and treatment modalities are the same, so reports of resistance in this species are highly relevant. Treatment failure of multiple doses of 0.2 mg/kg ivermectin was first reported in *P. ovis* infestation of Belgian Blue cattle [55]. An investigation of these treatment failures by Lifschitz and colleagues [56] showed that altered pharmacokinetics was not a contributing factor, as drug concentration and distribution to the skin was measured as adequate in these animals following subcutaneous injection. In Europe, macrocyclic lactone-resistant *P. ovis* was confirmed in 12 of 16

cattle farms in Belgium and the Netherlands, as determined by mite reduction counts. In some farms, infestation was persistent despite more than five rounds of treatment, which parallels observations of ivermectin treatment failure in crusted scabies [57]. The emergence of moxidectin resistance in *P. ovis* has also been identified in multiple farms across the United Kingdom and confirmed by *in vitro* bioassays similar to those employed for *S. scabiei* [58]. In a separate survey, mites collected from farms with poor moxidectin outcomes had highly variable responses to moxidectin, ivermectin and doramectin, and on average had significantly lower mortality relative to acaricide naïve mites from an experimental population. However, it was notable that some poor responding farms had mites that were still highly susceptible *in vitro,* suggesting that improper application or management also likely played a role in treatment failures [59]. *In vitro* studies on *P. ovis* collected from 'resistant' farms in the Europe study could not differentiate sensitive from resistant mites, with all LD_{50} values exceptionally high, but there is insufficient data to support whether this is due to experimental variability or true biological factors [57]. Collectively, the above studies unequivocally demonstrate the emergence of both ivermectin and moxidectin resistance in *Psoroptes ovis* and is a warning that judicious use in humans is critical to prevent a similar situation in scabies.

The high levels of permethrin resistance observed in head lice have led to the need for alternative treatments. With oral application, ivermectin is an obvious attractive choice. Consequently, in recent years ivermectin has become increasingly popular in many countries and its efficacy supported by randomised controlled trials [60]. However, given the history of resistance emerging in this organism, and to this drug, it is not surprising to see reports already arising. A 2014 case report from two villages in Senegal, where a high prevalence of lice exists, showed the failure of ivermectin in several individuals despite two 400 μg/kg doses [61]. Lice were collected from two of these patients for molecular studies of potential ivermectin resistance mechanisms, with mutations, transcriptional and proteomic changes identified [62] (see Sect. 27.5). This rapid emergence of resistance in this case is interesting, as ivermectin had not been used for head lice in this country previously; however, mass drug administration had historically been used in the region for the control of onchocerciasis; thus, lice may have had 'off target' exposure, indeed at subtherapeutic concentrations, meaning that selection for resistant lice had been occurring long before this intended clinical application.

27.4 Permethrin Resistance Mechanisms

27.4.1 Voltage-Gated Sodium Channel Alteration

Pyrethroid insecticides exert their effect by binding to arthropod neuronal voltage-sensitive sodium channels, where they cause irreversible, prolonged depolarisation and eventual paralysis, often termed 'knockdown'. Hence, resistance to pyrethroids is also known as 'knockdown resistance' or 'kdr'. Genetic mutations in transmembrane domains of the *Vssc* gene resulting in permethrin resistance are well

characterised in many insects, ticks and mites. Mapping of sodium channel mutations from resistant insects and mites in a review by Van Leeuwen [63] shows 'hot spots' around transmembrane (TM) subunit 5 and 6 of domain II, and subunit 6 of domain III. The *Sarcoptes Vssc* gene sequence was first sequenced in 2006 [17]. Genotyping of the permethrin-resistant laboratory isolates of *S. scabiei* var. *canis* subsequently identified an SNP (G1535D), which corresponds to TM subunit 6 of domain III. A high-resolution melt PCR assay method was applied to survey for this variant with resistant canine mites readily differentiated. While only limited analysis has been done, no resistance-associated variants in human derived mites have been identified in Australian populations [17].

The only other attempt to genotype scabies mites for this variant comes from a French survey of 40 patients, where individual mites were sequenced in resistance-associated regions of domains II and III of *Vssc* [64]. No mites were shown to contain the G1535D mutation, nor other resistance-associated SNPs in these regions. This result was not surprising, considering that ivermectin and benzyl benzoate have historically been the preferred treatments in France, so there is little selection pressure on esdepallethrin (the pyrethroid of choice in France). Given the increase in reported permethrin treatment failure in Europe, more extensive genotyping for sodium channel gene mutations would be of considerable interest.

27.4.2 Metabolic Detoxification and Other Mechanisms

Enhanced detoxification and metabolic clearance by the parasite are also associated with permethrin resistance. This may occur in conjunction with sodium channel insensitivity, or in isolation [65]. Three main enzymatic families have been implicated – esterases, glutathione S-transferases (GSTs) and P450 monooxygenases. These have been explored in the permethrin-resistant *S. scabiei* var. *canis* laboratory population via *in vitro* assays and direct measurement of enzyme levels. Esterases were increased by seven-fold, GSTs by four-fold, and P450s by two-fold in resistant mites [13]. In *S. scabiei* var. *hominis,* where increased *in vitro* survival times to permethrin were observed (Table 27.1), increased transcription and enzyme activity of mite GSTs was also demonstrated [16]. Importantly, the addition of esterase inhibitor and insecticide synergist piperonyl butoxide (PBO), and GST inhibitor diethyl maleate (DEM) effectively restored *in vitro* permethrin sensitivity in both studies [13, 16]. This suggests that the deployment of synergised pyrethroid products could be useful in combating increasing prevalence of resistant scabies.

27.5 Ivermectin Resistance Mechanisms

Compared to permethrin, the molecular mechanisms of ivermectin resistance are more complicated and remain largely unresolved despite decades of research [66]. This may be because macrocyclic lactones exert their effect on more than target site (interacting with numerous ligand-gated ion channels), and indeed appear to have

different mechanisms of action depending on the parasite. Recent whole genome studies in filarial nematodes confirm that ivermectin resistance is a complex, multigenic trait. In arthropods, there are fewer studies, but more evidence supporting the association of specific molecular candidates. The main lines of investigation in terms of ivermectin resistance are summarised below.

27.5.1 P-Glycoprotein and Other ABC Transporters

Increased drug efflux mediated by members of the ATP-binding cassette (ABC) transporter P-glycoprotein (Pgp) family was one of the first proposed mechanisms for ivermectin resistance. It was understood that ivermectin was a substrate for mammalian P-glycoprotein, as this protein is essential for maintaining blood brain barrier integrity, evidenced by the fact that mice and collie dogs carrying a mutation (*mdr1a-)*causing P-glycoprotein deficiency suffer from ivermectin neurotoxicity [67, 68]. Thus, it is a logical hypothesis that parasite-specific Pgps can mediate ivermectin resistance. Early support for this came from studies of ivermectin-resistant *H. contortus* where increased Pgp expression was observed [69]. This has since been confirmed in numerous other studies in both field and *in vitro* exposed populations of *H. contortus* [70] and in other ivermectin-resistant nematodes of livestock. Conversely, *in vivo* studies of Pgp expression levels in laboratory selected IVM-resistant *H. contortus* found only modest upregulation of Pgps, insufficient to explain the high levels of resistance observed [71]. Further candidate gene approaches in nematodes have identified polymorphisms and changed expression of Pgp and other ABC transporters; however, no single responsible gene has been identified.

In *S. scabiei*, increased expression of a Pgp was detected following ivermectin treatment in a crusted scabies patient with a history of developing ivermectin resistance [16]. While these mites were not phenotypically defined as resistant, *in vitro* survival to ivermectin had increased over the course of treatment (Sect. 27.2) [27]. Similar associations have been observed in other mites and ticks, although studies are not extensive. The expression of Pgps is increased in ivermectin-resistant cattle ticks [72]. Partial reversal of abamectin resistance via application of the Pgp inhibitor verapamil was conferred in the mite *Tetranychus cinnabarinus* which suggests involvement of Pgps, but neither mutations nor expression changes between sensitive and resistant isolates were identified in the two Pgps analysed. However, Pgp ATPase activity was increased, as was Pgp expression after *in vitro* exposure to sublethal concentrations of abamectin [73]. While Pgp has received much attention, the potential contribution of other ABC transporters should not be overlooked. Increased expression of the Multidrug Resistance Transporter (MRP) protein ABC-C4 has been identified as a transporter of ivermectin in the body louse *P. humanus* [74] and increased expression of this protein is observed after *in vitro* ivermectin exposure [75]. Studies of these transporters in ivermectin exposed *Drosophila melanogaster* showed similar results, and RNAi knockdown of Pgp increased ivermectin sensitivity in this model system [76]. Caution should be exercised in interpreting the

results of *in vitro* exposure experiments, and whether they appropriately represent resistance development *in vivo*. For example, ABC transporter expression changes were detected in the filarial nematode *Brugia malayi* following exposure *in vitro,* but not *in vivo* [77]. The same observations may be relevant to arthropods.

From the above, it appears that altered expression of ABC-transporters may facilitate enhanced drug efflux and confer at least partial resistance. The challenge with translation of such findings is that expression studies are not readily amenable to molecular diagnostic approaches. Access to viable samples and specialist handling of RNA is required, as is high level equipment and statistical analysis. However, if treatment failure is suspected in cases where large numbers of mites are available, these could be subject to genomic and transcriptomic analysis to assess the possible contribution of drug efflux. To our knowledge, this has not been attempted in scabies or other ectoparasitic disease.

27.5.2 Ligand-Gated Chloride Channel Alteration

The macrocyclic lactones exert their effect by binding to pentameric ligand-gated chloride channels, causing chloride ion influx, prolonged hyperpolarisation and subsequent paralysis. The endectocidal activity and relative safety margin of ivermectin in mammals is due to its high affinity for Glutamate-gated chloride channels (GluCls), which are specific to invertebrates. However, while the GluCls appear to be the primary target in many species, it is well established that other ligand-gated ion channels are also bound by macrocyclic lactones to varying degrees, both in mammals and invertebrates. These include channels gated by GABA, histamine and acetylcholine. A pH-gated chloride channel, first described in *D. melanogaster,* has been functionally characterised in *S. scabiei,* and found to bind ivermectin irreversibly [78]. Genetic polymorphisms associated with resistance or tolerance in scabies mite ligand-gated ion channels have not been investigated to date.

In nematodes, there are surprisingly few reports of field resistance being directly linked to GluCl channel mutations. Early indications showed selection at GluCl alleles in ivermectin-resistant *H. contortus* [79]. This has been supported by recent whole genome sequence analysis, confirming that variation of a GluCl gene (*Glc1)* was associated with ivermectin resistance in *H. contortus* globally [80]. However, to date the effect of specific GluCl mutations on decreased ivermectin sensitivity in *H. contortus* has only been predicted via laboratory models of functional expression rather than from directly resistant isolates [81–83]. In contrast, a mutation upstream of the critical TM2–3 region (L256F) was detected in ivermectin-resistant farm isolates of *Cooperia oncophora* and resulted in a 2.6-fold decreased sensitivity to ivermectin *in vitro* [84]. Manipulation of GluCls via site directed mutagenesis can readily confer high levels of ivermectin resistance in *Caenorhabditis elegans* [85] and mutations in the ligand binding domain of the *Glc1* gene have been identified in naturally ivermectin-resistant *C. elegans* [86].

In the case of *O. volvulus*, no variation in 'conventional' candidate resistance genes, including the GluCls has been identified. This is not entirely surprising, as

the prolonged effect of macrocyclic lactones on this parasite is via suppression of fecundity, not as a microfilaricide. It is this effect on fertility that appears to be altered in sub-optimal responders. Thus, it is fascinating that whole-genome sequencing of sub-optimal responding *O. volvulus* has revealed an association with alterations to acetylcholine neurotransmission, which is known to be of importance to egg laying in *C. elegans* [87]. It has been shown in *C. elegans* and other species that ivermectin can interact with nicotinic acetylcholine receptors (nAChRs), which are cationic channels [88]. Thus, this genetic association is plausible and adds yet another layer of complexity to the mechanisms of resistance in nematodes.

The contribution of ligand-gated chloride channels to macrocyclic lactone resistance are somewhat better defined in resistant arthropods. Mutations in the GluCls are mostly found in the TM 2–3 region which forms the ivermectin binding site, although there have been exceptions to this. The earliest report of GluCl mutations came from laboratory selected *D. melanogaster,* where a mutation in TM2 (P299S) conferred resistance to ivermectin [89]. In the two-spotted spider mite (*T. urticae),* there are five genes encoding GluCls. A323E mutation in the TM3 region of *GluCl1* was reported in abamectin-resistant isolates [90], and another mutation in the corresponding position (G326E) was identified in a second GluCl gene, *GluCl3* [91]. Functional characterisation of GluCl3 showed that this mutation completely abolished sensitivity to macrocyclic lactones, strongly implicating its role in resistance development [92]. Screening of spider mite populations has revealed this mutation is found at almost 100% frequency in abamectin-resistant populations in Greece and Korea [93]. Mutations in the TM3 region (A309V and G315E) have also been described and characterised in the abamectin-resistant diamond back moth, *Plutella xylostella* [94, 95].

In salmon lice (*Lepeophtheirus salmonis)*, where resistance to emamectin benzoate is common, decreased GABA-gated chloride channel and nAChR expression were identified in laboratory selected strains [96]. Independent genome sweeps of resistant and tolerant sea lice in both Atlantic and Pacific lice species have detected allelic selection at a linkage group containing a GABA-Cl, although higher resolution analysis of this region has not yet been reported [97, 98]. Sequencing of the field-resistant head lice cases from Senegal, (Sect. 27.2) revealed multiple GluCl mutations, with an A251V mutation in the TM3 region detected at the highest frequency [62]. To date, the effect of this, and the other mutations detected in head lice, have not been characterised functionally.

27.5.3 Metabolic Detoxification and Other Mechanisms

As is the case for permethrin resistance, metabolic detoxification is also understood to play a role in macrocyclic lactone resistance in some organisms. Transcriptional upregulation of GSTs has been identified in ivermectin exposed *S. scabiei* [16], and is also reported in several publications on abamectin-resistant *T. urticae* and *Panonychus citri* [99, 100]. Other detoxification pathways implicated in resistance include Uridine diphosphate glycosyltransferases [101].

Other mechanisms reported to be associated with macrocyclic lactone resistance in arthropods include reduced penetration via cuticular thickening in *D. melanogaster* [102], but this has not been explored in other organisms. Along with the GluCl mutations described in ivermectin-resistant head lice, a proteomic analysis of laboratory selected resistant body lice has been undertaken. Interestingly, a ten-fold downregulation in the complexins, which control neurotransmitter release was observed and verified via qPCR. Sequencing of the complexin gene in the resistant isolates revealed premature stop-codon mutations [103].

27.6 Conclusions and Future Research Directions

There are increasing reports of treatment failure in scabies, of which many appear to represent cases of bonafide resistance. This is especially true for permethrin in parts of Europe, and where treatment has been monitored by dermatologists or in an inpatient setting. The fact that live mites have been observed directly by dermoscopy following several rounds of permethrin treatment provides strong support for the emergence of permethrin resistance. While *in vitro* testing of these mites in survival assays would provide further evidence, most patients do not present with enough mites to permit the required controls and replication for these assays. They remain a good option for monitoring treatment efficacy in cases of crusted scabies or severe hyperkeratotic mange in animals. When investigating treatment failure, it is important to firstly ensure that the best evidence-based treatment regimens are being followed in the first place. Unfortunately, management of this disease remains inconsistent, both within and between countries [104]. Key challenges remain around one versus two doses, treatment of close contacts and the environment to distinguish between cases of newly hatched eggs, reinfection, or actual resistance. Here, patient education and clear messaging is critical.

More widespread molecular survey for permethrin resistance-associated *Vssc* mutations would be extremely valuable in light of these recent clinical observations. This requires the coordination of clinicians in collection of mites and researchers to undertake the assays, with protocols readily available [17, 64]. PCR tests are sufficiently sensitive to amplify single mites, or even possibly skin scrapings containing mite DNA. As PCR diagnostics are now becoming more readily available for scabies [105], so too could screening for permethrin resistance. Screening mites for other permethrin resistance mechanisms, such as metabolic detoxification is reliant on of the collection of large numbers of live mites and is thus not a viable option for most patients.

As ivermectin becomes more popular for the treatment of scabies, especially in community mass treatment, surveillance for developing resistance will become more important. It has been shown that resistance to ivermectin and other macrocyclic lactones can readily develop in cases of crusted scabies, in animal scabies, and in Psoroptic mange which has many similarities to scabies.

Macrocyclic lactone resistance is also very common in plant parasitic mites such as *T. urticae*. While there has been some promising early work done to define mechanisms of ivermectin resistance in *S. scabiei,* this has been restricted historically due to inadequate access to mites with defined resistance phenotypes, and also by insufficient genetic information about the scabies mite making candidate gene analysis difficult. It is also acknowledged that macrocyclic lactone resistance is a multifactorial trait, and this is also likely to be the case in *S. scabiei.*

One of these previous barriers has now been overcome in the recent availability of scabies mite genomic and transcriptomic data [106, 107]. This will enable complete annotation of the ligand-gated ion channel family, and functional assessment of which channels are likely to represent the physiological target of ivermectin and other acaricides in scabies mites. Since GluCl and GABA-Cl variations are commonly found in resistant lice and mites, it is well worth collecting scabies mites for survey of their potential contribution to resistance. Experience with organisms such as *H. contortus* and *O. volvulus* has shown that traditional candidate gene approaches may prove challenging. This is especially true for the ion channels, which are subject to extensive RNA editing to achieve receptor subunit diversity. However, next-generation sequencing and genome-wide analysis are powerful approaches that can potentially reveal novel genetic associations and allow for rapid screening of multiple resistance-associated variants. Thus, if large numbers of mites are available, and resistance is suspected, next-generation sequencing of these mites should be prioritised.

These suggested priorities for scabies resistance research are summarised in Box 27.1. The establishment of productive collaborations between clinicians and researchers, together with recent advancements in genomic data availability and molecular techniques, should facilitate a greatly enhanced understanding of the extent of, and mechanisms for the continued emergence of drug resistance in scabies. This will allow for more informed treatment and hopefully better outcomes in the future.

Box 27.1 Priorities for exploration of treatment failure in scabies

- Standardised assessment of reasons for treatment failure, with visualisation of post-treatment mites via dermoscopy where possible
- Collection of single mites for PCR and sequence analysis of the *Vssc* permethrin resistance gene, and candidate ligand-gated ion channel ivermectin resistance genes
- Annotation and functional characterisation of the ligand-gated ion channel superfamily in *S. scabiei*
- Collection of pooled mites from cases of suspected resistance for whole genome and/or transcriptome analysis

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Scabies Mass Treatment in Resource-Poor Countries

28

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28.1 Introduction

Scabies has traditionally been managed using a patient focused approach of treating the affected person and their family and close contacts. This approach is taken to prevent the chance of re-infestation of the person being treated.

Global data have highlighted that scabies is endemic in many resource-poor settings, and individual case treatment may not be appropriate to effectively and timely control high scabies levels in the community [1–3]. Most studies describing high scabies prevalence were conducted in medium or low human development index (HDI) countries, or disadvantaged populations within high or very high HDI countries. According to a global systematic review, highest prevalence of scabies was recorded in Papua New Guinea (71%) followed by Panama (32%) and Fiji (32%) [3].

Increasingly, it is being recognised that the approach of treating everyone in the community independently of whether or not they have the disease is appropriate to control scabies in endemic settings. Mass drug administration is a control strategy introduced by the WHO to control and eliminate NTDs [4]. Scabies was added to the list of NTDs in 2017 [5].

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28.2 Mass Drug Administration for Neglected Tropical Diseases

When the level of an infectious disease becomes endemic, individual treatment of cases is often impractical. Instead, it is more effective for everyone to receive treatment via a community-wide treatment approach, termed mass drug administration. This strategy involves the delivery of medications to a specified at-risk population, rather than targeting individuals with a clinical or confirmed diagnosis. It can be used in confined group settings, such as schools, prisons, hospitals and nursing homes, or expanded to cover districts, regions or even nations [3].

Mass drug administration has been adopted by the WHO as a strategy to control several neglected tropical diseases (NTDs) [6]. Over the past 20 years, it has been used for lymphatic filariasis, onchocerciasis, trachoma, yaws and soil-transmitted helminths. Examples include large global programme and the Onchocerciasis Elimination Programmes in the Americas and Africa.

NTDs cause life-altering consequences among resource-poor communities such as blindness (onchocerciasis and trachoma), lymphoedema/hydrocele (lymphatic filariasis), liver and bladder fibrosis and cancer (schistosomiasis), cholangiocarcinoma or bile duct cancer (opisthorciasis), anaemia, malnutrition and anaemia (soil-transmitted helminths), cutaneous lesions (leishmaniasis) and severe ulcers (Buruli ulcer). Scabies has recently been added to the WHO list of NTDs [5].

The five pharmaceutical pillars used in mass drug administration for NTDs are ivermectin, albendazole, azithromycin, diethylcarbamazine and praziquantel [7], with an estimated 700 million people receiving these essential medications per year. The combined cost of integrated NTD mass drug administration has been calculated to be roughly $0.50 per person per year [8].

As mass drug administration has been the key strategy in the elimination of a number of the major NTDs, the question arose as to whether a mass drug administration control strategy for scabies, and therefore its life-threatening complications, could be considered.

28.3 Mass Drug Administration and Scabies

Traditionally, the treatment of scabies, as mentioned in previous chapters, is focussed on treating the individual and their household contacts. Individual treatment is effective until scabies becomes endemic to a community, as individuals experience rapid re-infestation due to contact with untreated contacts [9]. Mass drug administration is used to manage scabies on a national level or for outbreaks in group settings. In higher-income countries, scabies is not generally perceived as a significant public health problem, except in localised situations such as refugee camps [10]. Outbreaks are more common among institutions and lower-income communities [11]. The model of treating a closed institution, using a mass drug administration strategy such as a school, prison or nursing home, is not dissimilar to treating isolated communities.

In a recent framework for scabies control, the WHO Regional Office for the Western Pacific led a consultation with experts who recommended mass drug administration [12].

- Where the population-based prevalence of scabies is estimated to be ≥10%. If school mapping is used, a higher prevalence threshold is suggested than for community mass drug administration. Evidence of its effectives in places with lower prevalence-based setting is unclear, however.
- Reach a minimal target coverage of 8% of the total population (for both oral and topical treatments).
- Implemented annually, consisting of three to five annual rounds, with impact assessments performed.
- Until the target community prevalence of infection <2% is reached.

The main goal of mass drug administration programmes is to reduce prevalence rates to a level that will interrupt transmission of the disease or to reduce levels to a point where they are no longer a major public health concern.

The use of mass drug administration for scabies control was initially documented in Panama in 1991 when permethrin was used to treat the local population on the San Blas Islands [9]. Topical permethrin mass drug administration led to a fall in scabies from 33% to 1%. However, the results were not maintained. The use of mass drug administration with topical 5% permethrin was also implemented in an Australian aboriginal community by Carapetis and colleagues [13]. A reduction in the prevalence of scabies was observed from 29.8% to <10% over a 25-month period. This striking reduction in prevalence is comparable to the outcome of a single ivermectin mass drug administration in the East Sepik province in Papa New Guinea over a 5 month period [14].

In 2003, five island communities in the Solomon Islands received oral ivermectin, except in children who weighed under 15 kg and pregnant women, who received topical 5% permethrin (see Figs. 28.1, 28.2, 28.3 and 28.4) [15]. The

Fig. 28.1 MDA programme for scabies being conducted in the Solomon Islands

Fig. 28.2 MDA programme for scabies being conducted in the Solomon Islands

Fig. 28.3 Community support for MDA in the Solomon Islands

Fig. 28.4 Skin examination during scabies MDA in the Solomon Islands

prevalence of scabies dropped from 25% to less than 1% at 3 years, and impetigo prevalence fell from 40% to 22%. The treatment not only improved quality of life but also showed decreased prevalence of haematuria among these Solomon Island communities [15]. Fifteen years later, follow up of the area showed that the high rates of scabies had not returned, although local conditions in this area had also changed [16]. This encouraging evidence suggested that mass drug administration could potentially control high prevalence of scabies in resource-poor communities.

28.4 Scabies and Mass Drug Administration Today

Oral medicines, such as Ivermectin, have made the mass drug administration approach more feasible, where adherence to topical treatments is more difficult to implement [17]. Participants can be witnessed taking a single medication, instead of going home and following the regime of applying permethrin cream. Topical therapies often require repeated applications, which are time consuming, difficult for those with limited mobility, impractical for single people to have cream applied to their back and can be associated with side effects such as skin irritation, itching and malodour.

A number of studies have explored the efficacy and safety of mass drug administration for scabies. These studies are summarised in Table 28.1 [12].

The Skin Health Intervention Fiji Trial (SHIFT) was a comparative trial conducted in Fiji by Romani and colleagues to determine the best treatment regimen for scabies control in highly endemic populations [19].

Three groups from small islands were randomised to either mass drug administration with ivermectin, mass drug administration with permethrin or standard care, giving permethrin cream to those with scabies and their household contacts. Topical permethrin was used for children under 15 kg, pregnant women and others for whom it was otherwise contraindicated. Ivermectin was found to be the superior treatment, with a reduction of 94% (from 32.1% to 1.9%), followed by permethrin-based mass drug administration by 62% (from 41.7% to 16.7%) when compared to standard care [7]. Ivermectin was effective, inexpensive and easy to administer (Fig. 28.5).

SHIFT revealed a sustained reduction in scabies and impetigo at 24 months which confirms the prolonged efficacy of ivermectin for use in mass drug administration strategies in these island-based communities [2].

Ivermectin-based mass drug administration for scabies was successfully scaled up to a population of 25,000 in the in the Solomon Islands by the team who led the azithromycin-ivermectin mass drug administration (AIM) trial [22]. A single round of mass drug administration of ivermectin combined with azithromycin for trachoma control was carried out. Prevalence of scabies showed a reduction from 18.7% to 2.3% at 12 months and a follow-up survey showed the sustainability of interventions with both scabies and impetigo rates being significantly lower than at baseline at 36 months [21].

Table 28.1 Summary of trials of mass drug administration for scabies control [12]

Study site	Design	Size	Intervention	Doses of treatment	Baseline scabies prevalence	Prevalence at 12 months	Reduction in scabies prevalence at 12 months	Reference
Panama	Single arm	756	Permethrin MDA and continuous surveillance and treatment of cases	1 dose for all participants	33%	1%	AR 32% RR 87%	[18]
Solomon Islands, Lau lagoon	Single arm	915	Ivermectin MDA and continuous surveillance and treatment of cases[a]	1 dose for all participants	25%	1%	AR 24% RR 96%	[15]
Fiji, SHIFT study	RCT	2051 in three arms	1 Ivermectin MDA 2 Permethrin MDA 3 Routine care	1 dose for individuals without scabies 2 doses for individuals with scabies	1 32.1% 2 41.7% 3 36.6%	1.8% 16% 18.8%	1. AR 30%, RR 94% 2. AR 25.7%, RR 62% 3. AR 17.8%, RR 49%	[19]
Australia, Northern Territory, Galawinku tribe	Single arm		Ivermectin MDA	1 dose for individuals without scabies 2 doses for individuals with scabies	4%	9% (prevalence reduced to 1% at 6 months)		[20]
Solomon Islands, AIM trial	Single arm	26,372	Ivermectin MDA	2 doses of treatment for all participants	18.7%	2.3%	AR 16.4% RR 88%	[3]

Study site	Design	Size	Intervention	Doses of treatment	Baseline scabies prevalence	Prevalence at 12 months	Reduction in scabies prevalence at 12 months	Reference
Solomon Islands, AIM trial	RCT	1291 in two arms	1 Ivermectin MDA 2 Ivermectin and azithromycin MDA	1 dose for individuals without scabies 2 doses for individuals with scabies	1 11.8% 2 9.2%	1% 0.7%	1 AR 10.8%, RR 91.5% 2 AR 8.5%, RR 92.4%	[21]

AIM azithromycin-ivermectin MDA, *AR* absolute reduction, *MDA* mass drug administration, *RCT* randomised controlled trial, *RR* relative reduction, *SHIFT* Skin Intervention Fiji Trial

[a]Ivermectin MDA includes topical permethrin treatment for individuals with a contraindication to ivermectin, including small children and pregnant women

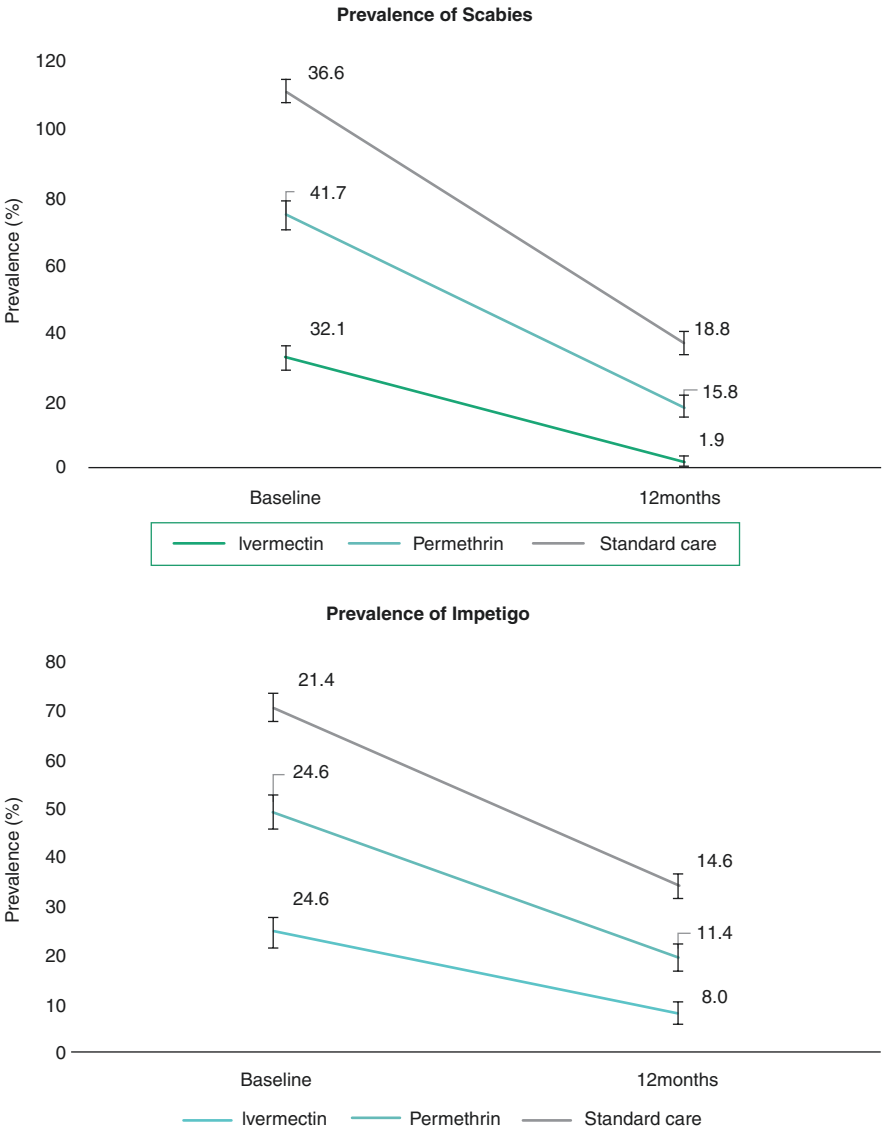

Fig. 28.5 Prevalence of scabies and impetigo at baseline and 12 months from the SHIFT trial in Fiji [19]

Although many of the studies were conducted in island populations, implementing a rapid-large scale mass drug administration for scabies has since been carried out in Ethiopia by the Ministry of Health, where the campaign covered over nine million people in 2018 [23]. This has been the largest scabies mass drug administration campaign globally and of the 1, 738,304 people who received treatment, the vast majority (94%) received ivermectin, compared to topical permethrin and sulphur.

28.5 Integration with Other Mass Drug Administration Programmes

In the past, mass drug administration strategies have focussed on giving one medication at a time in stand-alone mass drug administration programmes. However, since the addition of scabies to the WHO list of NTDs, treating several neglected NTDs at the same time by targeting similar populations or programmes with similar strategies has become feasible (Table 28.2).

For example, azithromycin was added to an ivermectin-based mass drug administration for scabies and impetigo by Marks and colleagues [25]. A further study in the Solomon Islands assessed the impact of ivermectin-based mass drug administration on the prevalence of *Strongyloides stercoralis* in children [26]. The medications used have shown to have beneficial impacts on other diseases. Treating trachoma with azithromycin has the beneficial effect of treating yaws [27]. The use of ivermectin mass drug administration for lymphatic filariasis on scabies prevalence in

Table 28.2 The overlap between neglected tropical diseases and their treatments [24]

Neglected tropical disease	Medication
Scabies	**Ivermectin**
Onchocerciasis	**Ivermectin**
Lymphatic filariasis	**Ivermectin** +/− Albendazole + Diethylcarbamazine
Strongyloidiasis	**Ivermectin** Albendazole
Soil transmitted helminths Ascariasis, trichiasis, whipworm, hookworm	Albendazole Ivermectin
Cysticercosis	Albendazole + corticosteroids
Echinococcosis	Albendazole
Trachoma	Azithromycin
Yaws	Azithromycin Penicillin
Schistosomiasis	Praziquantel
Leishmaniasis	Cutaneous – Supportive therapy Amphotericin B
Buruli ulcer/*Mycobacterium ulcerans*	Rifampicin + streptomycin/clarithromycin/ moxifloxacin
Chagas disease/*T. Cruzi*	Nifurtimox Benznidazole.
Chromoblastomycosis	Itraconazole +/− terbinafine
Dengue fever	Supportive
Dracunculiasis (Guinea worm disease)	Mechanical removal
Fascioliasis	Nitazoxanide
Leprosy	Dapsone + rifampicin + clofazimine
Mycetoma – Actinomycetoma + Eumycetoma	Co-trimoxazole + amikacin Itraconazole
Rabies	Rabies vaccine + immunoglobulin Ribavirin

Tanzania [28] showed a reduction in the scabies prevalence from 4.4% to 0.84% after a single round of ivermectin. Although ivermectin treats scabies it may also be used as a component of the regimes used for filariasis and onchocerciasis control.

The use of ivermectin has also the added benefit of treating other ectoparasitic infections prominent in the Pacific Islands such as head lice. The use of ivermectin showed a reduction in louse infestation from 25.4% to 7.5% at a three-month follow-up [29]. This offers an incidental benefit of MDA with ivermectin for scabies control. Treatment for head lice has not traditionally been associated with MDA, but this highlights an additional, possible unplanned benefit.

Due to the effectiveness of ivermectin against a number of NTDs, seen in table 28.2, there is support for ivermectin-based mass drug administration to be designed to treat multiple diseases at once.

Recent studies are expanding on this concept and combining medications to form integrated mass drug administration control strategies, such as the co-administration of scabies and trachoma treatment in the Solomon Islands combining azithromycin and ivermectin in a population of over 25,000 people. In addition, ivermectin use in both onchocerciasis and lymphatic filariasis programmes in Africa has provided a platform for exploration of scabies control where these diseases co-exist [30, 31]. Recent studies are looking at treating scabies, lymphatic filariasis and soil-transmitted helminths in a combination therapy regime, utilising ivermectin as the backbone [9, 32]. The triple combination of ivermectin, diethylcarbamazine and albendazole (IDA) is safe, effective and has the added benefit of also treating intestinal worms in addition to the three intended NTDs [9]. Adding ivermectin to pre-existing NTD programmes would be an effective way to treat scabies in areas where diseases co-exist. WHO now recommends IDA triple therapy in countries that are struggling to eliminate lymphatic filariasis [33, 34]. Expanding mass drug administration to treat more than one disease at a time improves its cost effectiveness and relieves pressure on the health sector [35].

A world-first national programme to treat Fiji and the Solomon Islands for scabies is currently being developed, and it is hoped that this will give global information for countries considering regional or national mass drug administration plans for scabies [36].

28.6 Strengths and Weaknesses of Mass Drug Administration for the Management of Scabies

In large populations, logistics are complicated and it may be challenging to achieve optimal treatment coverage. Resource-poor countries may not have the budget or infrastructure required to smoothly implement these much-needed mass drug administration strategies. An estimated 80% treatment coverage is recommended to successfully interrupt the transmission of scabies. When this is not achieved, participation fatigue increases and subsequent mass drug administration coverage decreases [13].

When using mass drug administration for scabies, healthy individuals without scabies will also be treated. A concern is that medication may be administered inadvertently to pregnant women. A recent meta-analysis however showed no adverse outcomes among 893 women who received ivermectin during pregnancy [37]. Another potential concern is that ivermectin resistance may occur with repeated mass drug administration. Although this has not yet been observed in clinical trials, resistance to ivermectin has been documented in patients with crusted scabies who had undergone over 30 treatments [38]. There are currently few anti-scabies drugs available; however, Moxidectin is a front runner currently in phase II of clinical trials [17].

Ivermectin has been used for many other ivermectin-based programmes delivering billions of doses. Recent studies have shown a sustained reduction in scabies and impetigo 2 years after mass ivermectin administration in Fiji [2] and 3 years out following Ivermectin mass drug administration in the Solomon Islands [4]. A further advantage is that Ivermectin is an oral medication, so health care workers can witness the participants take it compared to permethrin topical treatment, where direct observation can only be done with babies and small children. Mass drug administration can treat many diseases with one medication or even more diseases by combining medications within a mass drug administration programme. Mass drug administration is cost-effective for the health sector as it reduces complications secondary to scabies such as impetigo, sepsis, glomerulonephritis, skin and soft tissue infections and potentially rheumatic heart disease, and research is underway to assess this. Treating scabies on a large scale will reduce transmission, prevent recurrence rates and improve quality of life, reduce loss of time at school and increase productivity in many facets of life.

28.7 Conclusion

Mass drug administration is a control strategy used to substantially reduce scabies prevalence among the poorest populations. This strategy could be adopted to reduce community prevalence in endemic settings as a stand-alone programme or in combination with other diseases as a more cost-effective way to reduce the global burden of scabies.

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Scabies Management in Institutions

29

Jo Middleton, Jackie A. Cassell, and Stephen L. Walker

29.1 Epidemiology of Scabies in Institutional Settings

Scabies is an infestation with the mite *Sarcoptes scabiei*, an ectoparasite mainly transmitted between hosts by skin-to-skin contact and less commonly fomites (specifically objects in contact with the skin/skin scales of an infested person) [1, 2]. Transmission is therefore aided by overcrowding [3]. As part of industrialisation from the eighteenth century onwards, residential institutions proliferated, and scabies became associated with orphanages, workhouses, hospitals and jails [4]. Today, whilst population-wide scabies prevalence is highest in the global south [3, 5], outbreaks remain a considerable public health problem globally in semi-closed institutions [6, 7]. These include residential settings for elderly people, other adults with care needs, and children; refugee camps and other settings for displaced persons; prisons; schools; hospitals; hostels for those experiencing homelessness. Such institutional spaces often share similar transmission drivers that are relatively uncommon in the lower prevalence wider populations they sit within. These can make scabies case detection and outbreak control even more challenging than they are generally, and often produce very high attack rates [6–9].

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In a retrospective analysis of institutional scabies outbreaks from 1984 to 2013 by Mounsey et al. [7], 83% of index cases were people with crusted scabies, average attack rate was 38% and outbreaks typically lasted for 3 months. Outbreaks were most commonly reported from 'aged care facilities' and hospitals (respectively $n = 40$; $n = 33$). Other institutional settings included prisons, workshops for individuals with disabilities, schools, kindergartens, orphanages and childcare centres. However, Mounsey et al. cautioned that the higher connection of healthcare professionals and/or academics to 'aged care facilities' and hospitals compared to non-clinical institutions (such as schools and nurseries) may have resulted in reporting bias. The rate of peer reviewed reports of institutional outbreaks remained relatively constant over 30 years [7], but wider surveillance data is insufficient to determine whether outbreak incidence has changed over time. In England, institutional scabies outbreaks are commonly reported to Health Protection Teams (HPT) for support in management [10], although reporting is not mandated. We conducted a national audit of HPT records and found that 241 institutional outbreaks had been reported in 2016 (unpublished data) with residential care homes for elderly people being by far the most common type of institution requesting help (215 care home outbreaks reported) followed by childcare settings, hospitals and prisons. Requests also came from a military base, a private rehabilitation centre, a college and a hostel for men. There is thought to be underreporting of outbreaks to health authorities [11], potentially as a result of fear of stigma. Care home managers have expressed concerns to our team that outbreaks can cause reputational damage for their organisations, and Mounsey et al. found multiple outbreaks had resulted in just such negative publicity [7]. Scabies is a highly stigmatised condition [4, 12] with popular narratives linking it to inadequate personal washing [4, 13, 14], but this is not supported by epidemiological and experimental evidence [15].

29.1.1 Prisons, Detention Centres, Refugee Camps and Homeless Settings

More than 11 million people were thought to be incarcerated in penal institutions worldwide in 2018, 2.1 million in the USA alone [16]. Prisoners are at increased risk of a range of infections, including scabies [17, 18]. Prisons are densely populated inter-connected households, with frequent prisoner transfers both facilitating transmission between institutions, and interrupting diagnosis, case management, contact tracing and outbreak recognition [17]. Very high attack rates have been observed in jails, for example in one Tanzanian prison (pop. 1153 prisoners), 802 had ordinary scabies (69.5%) and 16 had crusted scabies (1.4%) [19]. Scabies prevalence in Polish prisons from 2001 to 2015 has been estimated as 2.3% [20]. In Cameroon, 32% of prisoners in three prisons had scabies March–August 2014; the most crowded prisons had significantly more cases, and sharing clothes/bedding, and cells with over ten detainees were both independent risk factors [21].

Scabies is a common problem in institutional settings for refugees, asylum seekers and other vulnerable migrants worldwide [9]. In German asylum seeker shelters

it was the third most regular category of outbreak 2004–2014 [22]. During large scale migration to Europe in the 2010's outbreaks were widespread in reception centres [23–25] and refugee/migrant camps both formal and informal [9]. Up to 40% of those attending a clinic in one informal camp in France were reported to have scabies [9], and it has been recorded as the most frequent dermatological presentation in refugee spaces in Europe [26], the Middle East and West Africa [27–29]. For example, in Cham Mishko camp in Kurdistan 45% of those who attended a dermatology clinic 2018–2019 (n = 1300) were diagnosed with scabies [27]. Healthcare staff who had treated scabies or managed associated outbreaks in refugee/migrant camps in seven European countries described camps as ideal environments for scabies transmission and identified barriers to management [9]. These barriers included: overcrowding; inadequate medical supplies; lack of privacy for examinations; substandard or non-existent facilities for washing clothes to reduce re-infestation; language barriers; interruption of repeat treatments and contact tracing due to population movements; reduced health service seeking to avoid the stigma associated with scabies. Scabies rates among refugees were used to suggest there was a health threat to host communities [14], and this stigmatising narrative was used to justify evictions [9].

Individuals experiencing homelessness are affected by high scabies prevalence [30, 31], with skin issues including scabies being the leading catalyst for seeking medical attention [30]. Arnuad et al. [32] found in Paris that living in abandoned buildings was significantly associated with a diagnosis of scabies, whilst those living in hostels for the homeless had lower prevalence than those 'sleeping rough' (0.4% and 5.4%, respectively).

29.1.2 Adult Healthcare Settings

Adult healthcare settings such as hospitals and care homes for older people are vulnerable to scabies outbreaks [6, 33] due to a range of intersecting factors. These include density of potential hosts; movement of infectious individuals between settings; frequency of manual handling by multiple care staff caring for many clients or residents. The age and clinical status of those being cared for may predispose to high mite-loads and delay or error in diagnosis and treatment [6, 8, 34]. Dementia or other cognitive impairment may limit ability to communicate symptoms and intensify social contact behaviours as well as the need for care, whilst pre-existing skin conditions may lead to delay or misdiagnosis. In the United Kingdom, people over 85 years of age have been shown to have the highest rate of scabies of any age group [35]. A high proportion of these cases are likely to be in residential care homes for the elderly [6–8]. Delayed diagnosis of the index case is a recurring feature of care home outbreaks [8, 33, 36, 37], and has major implications for eventual outbreak size [6, 38].

Our research team conducted the only prospective study of the epidemiology and clinical features of scabies outbreaks in care homes for elderly people [6]. Across outbreaks in 10 homes we examined 230 residents (76% female; 68% with

dementia; median 86.9 y (IQR 81.5–92.3)). Per home a median seven residents were diagnosed (IQR 3–10; range 2–11), with a total of 61 residents (27%) diagnosed with definite, probable, or possible scabies. Crusted scabies cases are highly contagious (Sects. 29.3.1 and 29.3.2) and four of the ten homes had at least one such case. Eight had staff diagnosed with scabies in addition to residents. Overall diagnostic delay was a median 22 d (7.5–186). Dementia was significantly associated with a scabies diagnosis (odds ratio [OR] 2.37 [95% CI 1.38–4.07]), and these residents were often considered asymptomatic by staff, probably due to their lack of ability to communicate scabies symptoms. Their higher odds of developing scabies may have been mediated not only by need for greater physical touch by staff, but also reflect altered patterns of behaviours. For example, due to a reduction in the social inhibition against touch and/or confusion about the identity of individuals those with dementia can have high rates of skin-to-skin contacts with other residents; from casual hand-holdings to sexual actions [39, 40]. In addition, non-normative patterns of movement around care homes, often stigmatised as 'wandering' [41], are likely to increase exposure to affected individuals, as are non-normative uses of spaces (for example, entering others temporarily uninhabited rooms and sleeping in the beds). Infestation may also be supported by cognitive impairment through decreased mite removal by scratching [42].

The clinical presentation in this setting (signs summarised in Fig. 29.1) differed compared to 'classical' descriptions heavily based on younger age groups. Less than half of the residents had visible burrows, whilst over half only had signs of scabies on areas normally covered. Over half were asymptomatic and of the 16 diagnosed residents who had complained about symptoms, only nine had complained of itch. Staff had not noticed skin signs in 20% of the subsequently diagnosed residents. This overall picture differs substantially from what clinicians may understandably expect based on scabies in children and younger adults (for example, see Rooks Textbook of Dermatology [43]). We interviewed 21 primary care physicians about how they would normally examine residents for scabies in care homes. They were unanimous they would begin by examining the hands: '*on their hands mainly and anywhere that they are complaining of an itch*'. One responded to the question of how they would select individuals to examine: '*I would examine people who are complaining of itching, scratching or people that the nurses are concerned about*' [34]. This mismatch between the clinical presentation in this setting and the diagnostic approach of primary care practitioners (based on the 'classical' description asking about itch, looking at the hands to assess likelihood, and expecting carers to be aware of cases) may in large part explain the substantial diagnostic delays associated with outbreaks in care homes for elderly people.

Many residents and staff were distressed by the outbreaks, particularly the mass treatments which typically involved repeated full-body applications of topical scabicide (for all living or working in the setting), showering to remove the scabicides,

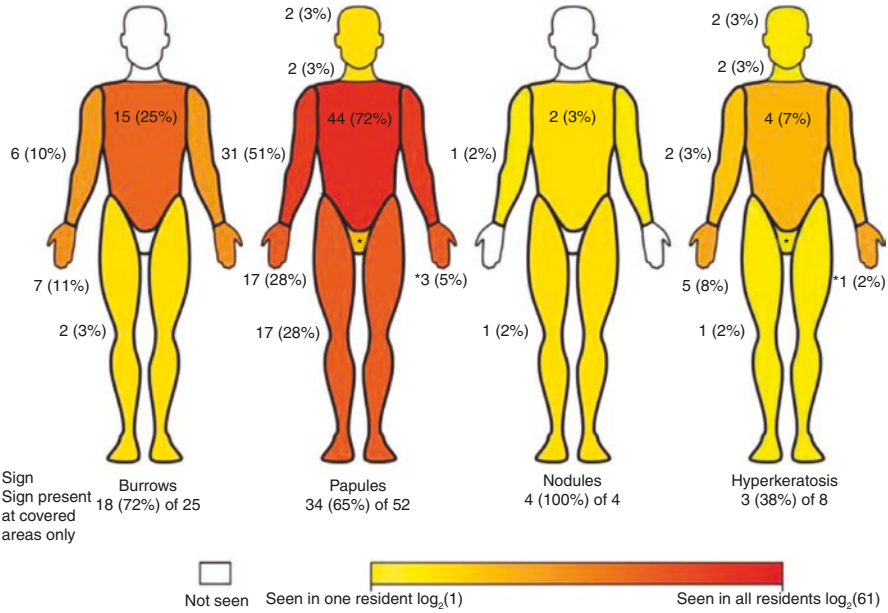

Fig. 29.1 Clinical signs of scabies in elderly care-home residents. Individual patient descriptions can be found in Cassell et al. [6]. Percentages in the figure are the proportion of residents with scabies who had that sign at that location. Percentages below the figures are the number of residents with the sign only in covered locations, out of all the people with that sign. Locations that would normally be covered by clothing are the upper limbs, torso (including back), lower limbs, and genitalia. The wrist was considered to be part of the upper limb, separate from the hands. (Image reprinted from [6] with permission from the authors who retain copyright)

and laundering of clothes and bedding. This was very labour intensive for staff, and many residents with dementia did not understand why these measures were being undertaken and found the process distressing. As one care home manager has put it: '*Scabies is very distressing for people with dementia, they don't understand why they are so itchy, and why we are covering them in cream and showering them* [8]. Scabies was recorded on one residents' death certificate as a significant contributing condition. Two of the ten homes had experienced previous scabies outbreaks in the preceding decade.

Scabies outbreak risk in hospitals varies depending on type of secondary care provided [33]. A nationwide survey in Japan (741 hospitals responding, 41.3%) found 333 hospitals (44.9%) in 2004 had ≥1 patients with scabies, 159 had experienced outbreaks. Higher bed numbers and presence of acute and long-term wards were both associated with elevated risk [44]. Hospitals, like residential care facilities, experience repeated outbreaks. New admissions contribute but considerable subsequent transmission is by infested staff or via fomites (when a crusted scabies

case is present). For example, three outbreaks were experienced over 17 months in a respiratory ward in Taiwan, many of whose patients were unconscious and on mechanical ventilation, needing regular re-positioning and bathing [45]. One of the outbreaks, which involved an individual with crusted scabies, had an attack rate of 20.7% (35 cases: 30 patients, 4 personal care workers, 1 nurse). A subsequent systems analysis indicated transmission hazards included: late diagnosis of index; infected staff; failure to disinfect a room after use by patient with crusted scabies; shared moving and bathing equipment. Chuang et al. [45] state that following this analysis an integrated systems intervention resulted in no reappearance of outbreaks for more than 5 years. Health Care Workers (HCWs) who regularly handle patients are at higher risk of becoming infested and contributing to transmission. In a 940-bed acute-care British hospital risk factors for being infested among exposed HCWs included being a physical therapist, nurse, or other HCW with extensive physical contact with infested patients (OR, 4.5; CI_{95}, 1.26–17.45) [46]. Similarly, in one Spanish nosocomial outbreak 41 HCWs in the affected ward (17%) were infested, but also 3 of 18 (17%) hospital stretcher-bearers in contact with the ward's patients, and an ambulance service member who transported the presumed index [47].

Careful cross-institutional contact-tracing has shown that outbreaks in care homes and hospitals are complex and are linked with infested patients or staff moving between settings. An outbreak in the Netherlands involved linked cases across ten organisations: two agencies providing care workers, four care homes, two sheltered accommodations, a general hospital, and a specialist travel agency for people with learning or mental health disabilities. The index case was admitted to a hospital neurological ward, and 46% of the subsequent cases were associated with more than one healthcare setting or other scabies case. Outbreak response involved treating more than 1600 contacts [48, 49].

29.1.3 Child and Young People's Establishments

Children and youths are affected by a high-burden of scabies (Chap. 18), particularly in the global south [3]. Related institutional outbreaks can have very high attack rates (e.g. 87% in Thai orphanages; 62% in a Bangladeshi religious school; 33% in a Turkish orphanage; 31% in a Malaysian welfare home [50]). Here we are primarily talking about institutions for those <18 y, but in some parts of the world secondary educational institutions may cater to age groups through their 20s. As with older age groups, highly contagious cases of crusted scabies may be core-transmitters in childhood outbreaks [51]. Even in long-industrialised nations scabies is not uncommon in children and youths [52–54], among whom prevalence has been observed to broadly increase with age [35] as they enter and spend greater amounts of time in pre-schools and schools. In addition to simple density, data from eight European countries has shown that in schools a higher proportion of contacts are physical than in most adult workplaces, and this can be expected to enable increased transmission of infectious diseases [55]. Infestation of carers can also be important; a study of an outbreak in a German kindergarten found the risk

ratio in nursery teachers was higher than in those they cared for (respectively 42·1, 10.5), with teachers who often hugged children having a probability of scabies 4·4 times greater than those who did not [56]. Children who preferred their own soft toys, rather than shared ones, had a lower probability of infestation. This may suggest transmission via fomites, though play choices may be proxies for social contact behaviours which impact risk via skin-to-skin contact. During bed-sharing close social physical contact enables *S. scabiei* to move between hosts, as does (to a lesser extent) bed-clothes acting as fomites [2]. Sibling bed-sharing was the norm in the global north until recently [57], and the cultural change towards children sleeping separately may be responsible in part for lowering rates of paediatric scabies. However, bed-sharing is still widely practiced, including in institutions, where it can be a driver of transmission [50]. Among youth scabies is often sexually transmitted [58, 59], and this should not be discounted within institutional outbreaks.

29.2 Approach to the Assessment of Risk and Control of Scabies in Institutional Settings

Institutional settings are diverse, but with many intersecting risk factors. Key to prevention and to control of outbreaks is a systematic approach to assessing the transmission drivers to be controlled in specific settings. We address this before moving on to interventions to prevent or manage outbreaks, including the choice of treatments.

29.2.1 An Approach to Assessing Scabies Transmission Drivers in Specific Institutional Settings to Guide Intervention and Treatment

There are many guidelines for management of institutional scabies outbreaks, mostly developed by sub-national health bodies or non-governmental organisations and for specific settings which are then often extrapolated to other settings. A contents analysis of 20 such guidelines found that basic information about scabies biology necessary for outbreak control, and recommendations for action, both varied widely and often contradicted each other in key dimensions [10]. This may be explained by a lack of relevant expert review, but also the weak evidence base on institution level control measures. Whilst more has been published on outbreaks in care homes for elderly people, there are no randomised controlled trials and studies are generally of low quality [60]. Settings vary greatly, and none will have a strong evidence base for any detailed approach to prevention and control of scabies. To support the practitioner in tailoring an effective approach to a specific setting, in this chapter we provide:

1. An approach to the epidemiological assessment and identification of transmission drivers in any setting, and,
2. Specific guidance on what control measures to take to reduce scabies transmission drivers once identified.

29.2.2 The Importance of Epidemiological Assessment of Institutional Settings

The recognition of scabies outbreaks is complicated by the natural history of the infestation, even in its 'classical' form. The incubation period between entry of scabies mites into skin, and the onset of itching and skin lesions is around 4–6 weeks, though it can be a matter of only 24 h for repeat infestations (Chap. 4) [2, 61]. The diagnosis might not be confirmed even when done by experts [6], whilst psychogenic itching and scratching in response to other people scratching [62] further complicates the picture. By contrast with an outbreak of gastrointestinal infection, it will not be immediately obvious who is currently infected, as symptoms and signs emerge over a long period, even where easily ascertained. At the time an index case or outbreak of scabies is first recognised, the number of people already infested will be uncertain. Control measures that will minimise onward transmission, ensure treatment of those most likely to be infested, and reduce symptom burden need to be chosen quickly. In settings where quick elimination is unlikely to be possible, consideration needs to be given to how transmission drivers can be reduced through structural changes. This requires identification of the likely local transmission drivers, based on epidemiological principles.

29.2.3 Identification of Key Transmission Drivers in Institutional Settings

The key to identifying transmission drivers in an institution is to assess what drivers of the Basic Reproductive Rate (R_o) are present. R_o is the number of new infections generated by a single incident case in a population with limited or no immunity [63], as in the case of scabies [38, 61]. The magnitude of R_o is amplified by increases in any or all of:

the transmissibility of the infection per contact (β),
the rate of contact with infectious sources (c), or.
the duration of infectivity (D).
This is summarised in the equation: $R_o = \beta\, c\, D$

Identifying the characteristics of a setting which drive high values for β, c, or D is a key first step to considering what actions can be taken to minimise spread, and in the absence of an outbreak what priority should be given to early detection.

Table 29.1 details scabies transmission drivers in institutions and their impact on drivers of R_o. It sets out three broad areas of transmission drivers: (a) social and environmental, (b) host related, and (c) access to and quality of services and

Table 29.1 Classification of scabies transmission drivers in institutions and their impact on drivers of R_o

	Transmission driver	Transmissibility (β)	Contact rate (c)	Duration of infectivity (D)	Comments
Social and environmental drivers	High densities of potential hosts		+	+	In high density settings frequency of exposure prone contacts (generally touching) and duration may be increased by proximity. Note this may overlap with behavioural factors, e.g., bed sharing
	Staff/resident/visitor movements between semi-closed units		+/−		Movement in and out of institutions due to resident turnover, and staff/visitors moving in and out will increase risk of infection *ingress* and therefore contact with a new infection. However, it may or may not in itself have an impact on contact rates
	Fomites	+			This is likely to be a particular issue with cases of crusted scabies, where substantial environmental shedding of viable mites can occur
	Behaviours involving prolonged touch	+			Prolonged touch (including as part of care) increases the likelihood of mite acquisition in any skin-to-skin contact
Host drivers	Crusted scabies	+	+	+	Mite load is much higher in crusted scabies cases increasing transmissibility via skin-to-skin contact and increasing contact rate via fomites. Cases are often difficult to resolve with topical acaricides, prolonging duration of infectivity (unless patients die in part due to severe infestations)
	Immunocompromise			+	Immunosuppression may increase the period of infectivity in the absence of effective pharmaceutical treatment and is a risk factor for crusted scabies
	Cognitive impairment	+	+	+	Resident behaviour or requirement for additional care arising from cognitive impairment may increase the number of skin-to-skin contacts, whilst impaired ability to recognise and communicate symptoms leads to delayed recognition and care
	Communication difficulties			+	Inability to communicate symptoms, or to be understood when seeking to do so, may lead to delayed recognition and care

(continued)

Table 29.1 (continued)

	Transmission driver	Transmissibility (β)	Contact rate (c)	Duration of infectivity (D)	Comments
Access to/ quality of health and care services	Reduced access to treatments			+	Inadequate supplies of appropriate treatment (including oral ivermectin) will prolong duration of individual cases and risk greater outbreak size
	Diagnostic error or delay			+	Delay in diagnosis delaying treatment and prolongs duration. Corticosteroid treatment resulting from misdiagnosis can cause therapeutically induced immunocompromise risking crusted scabies
	Reduced access to laundry	+	+	+	Inadequate killing of mites on fomites (clothing, bedding etc.) will increase transmissibility and reduce effectiveness of mass treatments

interventions including treatments. These together provide a framework of what aspects of a setting need to be assessed, enabling the practitioner to identify the available interventions that can reduce the risk of avoidable transmission and enable early treatment to relieve symptoms.

29.3 Outbreak Prevention and Control Interventions

Individuals (residents, staff, or visitors) bring *S. scabiei* mites into an institution with them, often asymptomatically. If prevalence of scabies in the wider population is very high, ingress of infection may be so frequent that prevention to the point of complete elimination at any time will not be feasible. Here the focus needs to be on reducing internal structural drivers, and on early identification and treatment of cases and contacts which may include regular screening. In other settings, cases will only occasionally emerge and it may be more appropriate to focus on control through early recognition and prompt management. In this case, when an outbreak occurs, control aims at total elimination of *S. scabiei* from the institution through mass treatment to kill the mites living in the skin of exposed individuals, and where practical simultaneous environmental decontamination.

29.3.1 Interventions Targeting Social and Environmental Drivers

Table 29.2 indicates the various social and environmental factors that contribute to transmission and their expected presence in particular institutional types.

Host densities: In some settings resident and staff densities can be reduced without altering the overall size of the population, for example by utilising unused areas. Bed-sharing should be stopped where possible, at least whilst awaiting mass treatments. In places such as refugee camps and informally housed communities this may require provision of additional bedding and shelters, and ideally family groups should have access to their own dedicated space [9]. Under no circumstances should density be reduced by sending residents to other institutions, which is likely to lead to further outbreaks. Many institutions have common rooms (dining and recreation), and these can be temporarily closed to reduce mixing. However, it is important to be cognisant of the fact that institutions are people's homes (whether voluntarily or not) and issues of social liberty and wellbeing may outweigh the risk of continued scabies transmission.

Behaviours involving touch: During outbreaks skin-to-skin contact between residents and between residents and staff should ideally be reduced. However, in healthcare settings where considerable handling is required, this is difficult, and it should be taken into consideration that touch is an important aspect of caring. Gloves should be worn by staff when providing personal care and touching laundry and other potential fomites. Prompt hand-washing following handling may reduce somewhat the chance a carer becomes infested from a contact, but only as a result of mechanical action as there is no evidence hand-soap or alcohol-gel have any

Table 29.2 Social and environmental transmission drivers of scabies across institution types. Transmission drivers marked HC are those we are highly confident can be expected to be found in an institutional type (based on literature identifying them as such or our teams experience). MC indicates those we have medium confidence in expecting to be present in a particular type of setting (but for which we are unaware of published evidence)

Transmission drivers	Care homes for elderly people	Hospitals	Refugee camps & settings for displaced persons	Homes for those with learning disabilities	Prisons & detention centres	Homeless hostels	Children's homes	Schools	Your setting?
High densities of potential hosts	HC	HC	HC	HC	HC	HC	HC	HC	
Behaviours involving prolonged touch	HC	HC	HC	HC	HC		MC	MC	
Staff/residents/visitors moving between semi-closed units	HC	HC	HC		MC				
Fomites	HC	HC	HC			HC		MC	

effect on mites [15]. It is important people are made aware that wider behaviours involving touch (such as sex and contact sports) may also enable transmission, but in the absence of cases the possibility of contagion should not be used to curtail social interaction.

Staff/residents/visitors moving between semi-closed units: Screening of new members of institutional communities using skin examination at the time of admission may help to reduce the ingress of *S. scabiei*. This has been operationalised in Dutch refugee centres [24], and could be incorporated into general health screening on entry to some health and social care institutions (although it will not be possible to identify those without signs or symptoms in the early stage of infestation). Individuals with skin symptoms or signs should be assessed and PPE and other control measures used until a diagnosis is established. However, in some settings, this may be impractical (e.g. informal refugee camps [9]) and in others it may be considered overly-intrusive.

Once an institutional scabies outbreak has been declared, the following should be enacted, where possible:

1. Avoidable transfers of residents in and out of the institution should stop until at least the second round of mass treatment.
2. When only a section of an institution (e.g. floor, wing) is affected by an outbreak staff who handle residents working in that section should be cohorted as far as possible, i.e., should not work in other areas, and ideally if required to work in pairs staff should do so in consistent pairings. Similarly, residents should not move between affected and unaffected sections.
3. Continuation of some level of visitor access is usually socially necessary, but priorities for continued visits will depend on the institutional type. Temporarily avoidable outside visitors such as building contractors, entertainers etc. should be minimised, particularly those who work across at-risk institutions. All visitors should be made aware of the scabies outbreak and be given guidance on the control measures (such as halting skin-to-skin contact) they should adhere to so as to reduce risk of transmission.

COVID-19 outbreaks in semi-closed settings have been associated with staff movement between institutions. Most care homes we studied that suffered scabies outbreaks employed some staff on a casual basis (unpublished data), many of whom had to work in other homes to avoid underemployment. In all types of institutions reducing the number of workers with such employment conditions is likely to reduce the risk of ingress of *S. scabiei*.

Fomites: In most cases scabies transmission is likely to be skin-to-skin, but transmission is possible via fomites such as bedclothes when an individual has higher than normal mite load [2, 64–66]. This is a particular risk in crusted scabies (Sect. 29.3.2). Those not directly caring for residents may also potentially be affected, as reported infestation of laundry workers suggests [67]. *S. scabiei* can survive off-host and retain the potential to infest for considerable time, and live mites have been found in dust samples from bedroom floors, soft furnishings and beds of individuals

with scabies [68, 69]. Outbreak control may fail without decontamination of institutional environments even when appropriate mass treatment has been used.

Care should be taken cleaning areas individuals with crusted scabies have used. Avoid cross-contamination from affected to unaffected areas by using different cleaning equipment (such as vacuum cleaners) or by ensuring they are decontaminated. In vitro work showed some pyrethroid biocides were effective against *S. scabiei* [70], but to our knowledge no studies have evaluated their acaricidal efficacy or dose safety in environmental decontamination. The best approach for decontamination of clothing, bedding and soft furnishings is to expose fomites to heat levels effective at killing mites: washing or drying at ≥50 °C, minimum 10 min (detergent not required); or -10 °C, minimum 5 h [71]. Where this is not practical isolating fomites in plastic is also effective, but can take 3–8 days depending on climate [71] (detailed in Fig. 29.2). In settings such as refugee camps people may lack spare clothing, but this problem has been overcome by clothes donations or the creation of an inventory of cleaned 'rental' clothes individuals use whilst theirs are bagged-up [9]. Even in well-resourced institutions this scale of simultaneous

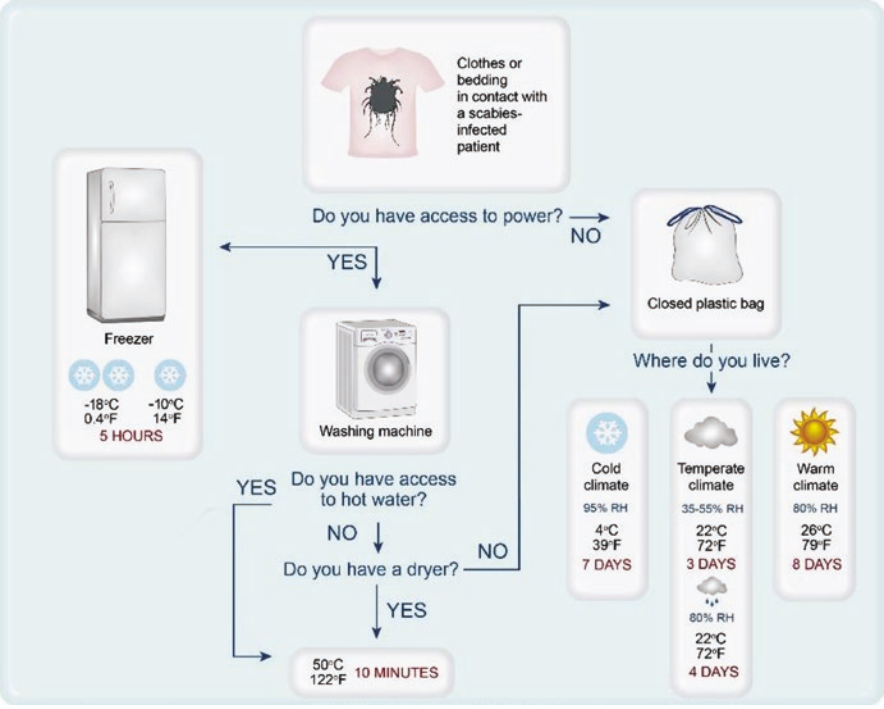

Fig. 29.2 Flow chart outlining the proposed strategies for the environmental control of human scabies. RH, Relative humidity. This figure originally appeared in an article published in Journal of the American Academy of Dermatology, Bernigaud et al., How to eliminate scabies parasites from fomites: A high-throughput ex vivo experimental study, p.241–245, Copyright Elsevier (2020) [71]

decontamination (carried out alongside mass treatment) can be challenging due to increased staffing requirements, the sheer volume of laundry to be processed, and the need for sufficient clean laundry to change all the beds. Sufficient staffing, logistics and supplies should therefore be carefully planned in advance, and in some situations may simply not be possible.

29.3.2 Interventions Targeting Host Transmission Drivers

Table 29.3 indicates the host factors that contribute to transmission and their expected presence in particular institutional types.

Crusted scabies and immunocompromise: People with crusted scabies are highly contagious, harbouring up to 4700 mites per gram of hyperkeratotic crust [72]. Crusted scabies is usually less pruritic, is difficult to diagnose for those unfamiliar with it (contributing to diagnostic delay), and treatment responses may be slower or reduced. All factors which may contribute to continued transmission. Case treatment (particularly with oral ivermectin) is discussed in Sect. 29.3.4 and covered elsewhere (Chap. 25). To enable outbreak control those with crusted scabies should be rapidly treated, and environmental decontamination carried out where possible (Sect. 29.3.1). They should also be isolated from others. Risk factors for crusted scabies cases very often progress as a result of pre-existing immunocompromise (age; corticosteroid treatment; HIV; etc.). Immunocompetent individuals may develop crusted scabies so a high index of suspicion should be maintained given the potential for these individuals to act as core-transmitters [61, 72, 73].

Communication difficulties and Cognitive impairment: Institutional screenings for scabies should not rely for case identification on symptomatic complaint by individuals as this may miss (1) those unable to communicate, (2) those with cognitive impairments which interfere with their recognition of symptoms, and (3) those avoiding disclosure due to stigma, fear or punishment or eviction. A full review including examination for physical signs is required (see Sects. 29.3.1 and 29.3.3). Individuals with dementia may be unable to follow infection control measures. For example, 'wandering' behaviours (such as finding a temporarily uninhabited room and sleeping in the bed thinking it is one's own) can enable wider spread of infestation across an institution than may otherwise be expected [74]. Under such circumstances locked-door segmentation of institutions may be required during outbreaks, even in settings where this may not be the norm. The logistics of outbreak control, particularly involving topical treatment, can be distressing for the cognitively impaired, so ways of supporting residents during the process need to be considered.

Language differences between staff, affected individuals, and other community members may be a major barrier to diagnosis and adherence with treatment and environmental decontamination measures [9]. Translators able to accurately convey clinical information are invaluable. If unavailable, pre-recorded voice recordings on mobile devices can be used to explain scabies treatment guidelines across many different languages; a tactic used by those managing scabies outbreaks at European border camps in Greece [9].

Table 29.3 Host transmission drivers of scabies across institution types

Transmission drivers	Care homes for elderly people	Hospitals	Refugee camps & settings for displaced persons	Homes for those with learning disabilities	Prisons & detention centres	Homeless hostels	Children's homes	Schools	Your setting?
Crusted scabies	HC	HC	MC	HC	HC	MC		HC	
Immunocompromise	HC	HC	HC	HC	HC	MC			
Communication difficulties	HC	HC	HC				MC		
Cognitive impairment	HC	HC		MC					

Transmission drivers marked HC are those we are highly confident can be expected to be found in an institutional type (based on literature identifying them as such or our teams experience). MC indicates those we have medium confidence in expecting to be present in a particular type of setting (but for which we are unaware of published evidence)

29.3.3 Interventions Targeting Transmission Drivers Related to Access to and Quality of Health and Care Services

Table 29.4 indicates factors related to access to and quality of health and care services that contribute to transmission and their expected presence in particular institutional types.

Reduced access to appropriate treatment: Even in countries with extensive supply chains sufficient quantities of drugs for mass treatments are often not immediately available. Where possible in advance of an outbreak at-risk institutions should set-up a single prescription-pharmacy supply for the whole institution to provide uniform supply. Given the common occurrence of re-emerging infestations after mass treatments if this is not already in place it is sensible preparatory step to be carried out immediately after presumed outbreak control. Use of oral ivermectin is likely to be more practical [75], which is discussed further in Sect. 29.3.4.

Diagnostic error and/or delay: Diagnostic error is common with scabies, and can lead to incorrect application of steroids which support development of crusted scabies (Sect. 29.3.2). Familiarity with scabies among clinicians and staff of institutions is key, and early detection will reduce eventual outbreak size. However, in those over 85 years of age, clinical presentation of scabies can differ from those familiar to many clinicians [6, 42, 76], as we outline in Sect. 29.1.2. Care homes for the elderly are the institution from which scabies outbreaks are most reported, and avoidable diagnostic error is often a significant feature [8]. Given care home residents with scabies might be asymptomatic and have subtle signs at covered sites, we recommend thorough and careful examination (particularly of individuals with dementia). Once a case is detected in a home we recommend the whole affected section is screened in this manner to determine if there is another case. If so an outbreak should be declared, screening (Sect. 29.3.1) continued to ensure an individual with crusted scabies has not so far been missed, and simultaneous mass treatments (Sect. 29.3.4) and environmental decontamination (Sect. 29.3.1) arranged. Early detection is the keystone to all other interventions. Though laboratory examination of skin scrapes for *S. scabiei* may provide confirmation of clinical diagnoses, given their low sensitivity [6] they should not be used to rule out diagnoses and delay or avoid outbreak control. More broadly, practitioners should be alert to the risk that the ramifications of declaring an institutional outbreak (‘*the nightmare of treating all the residents and nursing staff*’ as one described it [34]) may predispose to clinical ‘wishful thinking’ similar to that found regarding bacteraemia [77]. In addition, a further common barrier to prompt diagnosis in institutions is the stigmatising idea that scabies isn’t found in ‘modern’ clean institutions. This fallacy is long-standing. In a 1936 paper in JAMA titled ‘Scabies among the well-to-do’ a dermatologist laid out a catalogue of misdiagnoses among ‘the better feathered, the silver-spooned’, and quoted one doctor as remarking: ‘*I would have called it scabies myself if it hadn’t been I thought that was a disease no nice people ever had*’ [13].

Reduced access to laundry: Many health organisations still respond to scabies outbreaks with educational campaigns on personal washing. However, evidence

Table 29.4 Scabies transmission drivers related to access to and quality of health and care services

Transmission drivers	Care homes for elderly people	Hospitals	Refugee camps & settings for displaced persons	Homes for those with learning disabilities	Prisons & detention centres	Homeless hostels	Children's homes	Schools	Your setting?
Reduced access to appropriate treatment	HC	HC	HC	MC	HC	MC	MC	MC	
Diagnostic error and/or delay	HC	HC	HC	MC	MC	MC	MC	MC	
Reduced access to laundry		HC	HC		HC				

Transmission drivers marked HC are those we are highly confident can be expected to be found in an institutional type (based on literature identifying them as such or our teams experience). MC indicates those we have medium confidence in expecting to be present in a particular type of setting (but for which we are unaware of published evidence)

from experimental work and epidemiological studies strongly indicates scabies prevalence is not actually related to personal washing [15]. Nevertheless, providing Water Sanitation and Hygiene facilities can still be an important part of integrated action in settings where access may be restricted. Water supplies can aid laundry of fomites (Sect. 29.3.1) [9], and access to personal hygiene could be expected to minimise some of the secondary infections that often complicate scabies (Chap. 11) [5].

29.3.4 Considerations in the Choice of Treatments

Treatment guidance for individual cases and their close contacts (Chap. 24) and related issues (post-treatment itch; secondary bacterial infections, etc.) are covered elsewhere in this volume. However, where an individual case is diagnosed in an institution, it is important to maintain a high level of suspicion as it is very likely other cases are still to be identified due to the asymptomatic incubation period (Chap. 4) or misdiagnosis [6]. Following examinations throughout the institution (Sect. 29.3.3) where two or more cases are detected simultaneous mass treatment should be conducted. These must cover all in the affected part of the institution, including staff, and for greatest success be conducted with environmental decontamination (Sect. 29.3.3).

Topical acaricides are generally first-line treatment. Salavastru et al. [78] recommend 5% permethrin cream (repeated once after 7–14 days) or 10%–25% benzyl benzoate lotion (days 1, 2 and repeated after 7 days) left in place for 8–12 h. Other topical alternatives are discussed and choice may be guided by availability [78]. Repeat administrations are required as most acaricides are not ovicidal [79]. Follow-up treatment at the recommended intervals can kill those mites that have hatched following initial treatment, before they have sufficient time to develop to sexual stages and lay eggs themselves. Failure to carry out recommended repeats of mass treatment likely contribute to treatment failures in institutional outbreaks.

Topical mass treatment may not always be practical in institutional settings, particularly in refugee camps [9] and care homes for the elderly [75]. Oral ivermectin (200 μ/kg bodyweight, repeated after 7 days) [78] has been successfully used in Mass Drug Administrations (MDA) for community control of scabies in Fiji [80] (Chap. 28) and within institutions, predominantly prisons [19, 81] for which it is recommended by the International Committee of the Red Cross [18]. It is also increasingly being used to control other institutional outbreaks [24, 82, 83]. In 2019 the World Health Organisation added ivermectin for the treatment of ectoparasitic infestations to its list of essential medicines [75], but it is still underused for scabies control in institutions. This is in part due to ill-founded safety concerns about its use in the elderly [38]. The safety of ivermectin in the elderly is supported by a 2021 report of a scabies outbreak in a French long-term care facility in which no deaths were recorded 56 d after an ivermectin MDA (69 residents, median 90 y, IQR 84–94; 78% female) [82, 83]. Modelling also demonstrates early MDA with oral ivermectin is likely to significantly reduce institutional outbreak size, and therefore cost [38]. Even when topical scabicides are chosen for institutional MDAs, oral

ivermectin should still be considered in addition to topicals for individuals with crusted scabies (Chap. 25) [78]. In such cases, Salavastru et al. [78] recommend ivermectin (200 μ/kg of bodyweight) should be given on days 1, 2 and 8, and in severe cases days 1, 2, 8, 9, 15 +/− 22 and 29. This should be alongside the patient receiving topical scabicide daily for 7 days then twice weekly until cure.

In the care home outbreaks we observed in the United Kingdom most homes had to obtain individual prescriptions for their residents and staff from multiple primary care physicians based at different practices, and even when all prescriptions had been obtained further delays in conducting MDA often resulted from insufficient quantities of stock held by local pharmacies [6]. Care-givers in refugee/migrant camps in Europe reported that even where acaricides were available the sporadic supplies, often donation based, resulted in treatment regimens using multiple parallel medications. This caused confusion and reduced adherence [9]. Given these types of issues, choice of effective medication should be partly based on logistics of supply and sustainable consistent effective treatment.

29.3.5 Communication During Outbreak Control

Some communication issues regarding residents (cognitive impairment; language barriers) are outlined in Sect. 29.3.2. However, effective outbreak control in institutions requires clear communication to all those involved: residents, staff, and wider stakeholders. This must be carried out at each stage of the process from the declaration of an outbreak, through the planning and implementation of mass treatments and environmental decontamination, during the follow-up treatments, and when declaring an outbreak over. Residents and staff need to be made aware of what scabies is and the actions required. Stakeholders need to be informed that there is a scabies outbreak, what it involves, and that action is being taken. Clear communication will promote adherence, and may reduce anxiety and stigma.

29.3.6 Summary and Checklist

Scabies outbreaks in institutions are challenging to control, but early detection and comprehensive action can successfully eliminate scabies from institutions, or at least substantially reduce its burden when regular ingress of *S. scabiei* is inevitable from surrounding populations with high prevalence. To aid practical management, we conclude this chapter with a summary checklist of the key steps to take in responding to an institutional outbreak (Table 29.5). Details of how each step is actioned in any particular setting should be based on an assessment of local needs and transmission drivers as outlined in Sect. 29.2, and consideration of the issues around control interventions discussed above (Sects. 29.3.1–29.3.5).

Table 29.5 Summary checklist of the key steps to take in responding to an institutional outbreak

Stage	Action	✓
1. In advance	Conduct an epidemiological assessment of transmission drivers (Sects. 29.2–29.3.3)	
	Consider skin examination screening at admission (Sect. 29.3.1)	
	Consider reducing number of casual workers so as to reduce risk of ingress from other at-risk institutions (Sect. 29.3.1)	
2. Once a case is detected	Treat the individual (Sect. 29.3.4) and educate them and staff and visitors who care for them (Sect. 29.3.1)	
	If they are a crusted case rapidly treat (Sect. 29.3.4) and decontaminate their environment (Sect. 29.3.2)	
	Carry out a thorough and careful examination (particularly of individuals with dementia) of the whole affected section and **declare an outbreak where two or more cases are detected** (Sect. 29.3.3). In institutions with elderly residents, clinicians should consider the non-classic presentation in this age group (Sect. 29.1.2, Fig. 29.1, Sect. 29.3.3)	
3. Once an outbreak is declared	Ensure effective, accurate communication of the problem to residents, staff and other stakeholders (Sect. 29.3.5)	
	Seek outside public health and dermatology advice and assistance where available (29.1)	
	Stop avoidable transfers of residents in and out of the institution (Sect. 29.3.1)	
	Continue screening to ensure crusted scabies cases have not been missed (Sect. 29.3.3)	
	Compartmentalise institution, including staff cohorting, if only part affected (Sect. 29.3.2). Where cognitive impairment reduces adherence locked-door segmentation may be required (Sect. 29.3.2)	
	Reduce unnecessary visitors (Sect. 29.3.1)	
	Educate staff, residents, and visitors about role of touch in transmission, and explain and destigmatise the condition (Sect. 29.3.1)	
	Consider changes in the use of spaces to reduce density and closure of primary mixing spaces (such as common rooms), and discourage bed-sharing (Sect. 29.3.1)	
	Provide gloves for staff to wear when providing personal care and touching laundry and other potential fomites (Sect. 29.3.1)	
	Prepare for mass treatment of residents and staff: Ensure sufficient medical supplies, ideally uniform (Sects. 29.3.2, and 29.3.4), and staffing, including translation capacity if required (Sect. 29.3.2)	
	Prepare for decontamination: Ensure sufficient staffing and supplies are in place, including additional bedding and clothing (Sect. 29.3.1)	
	Consider if you intend to publish an outbreak report after control. If you do, given the low quality of existing data (Sect. 29.2.1) consider using the framework for data collection for observational studies of institutional scabies outbreaks [60] to improve the evidence base	

(continued)

Table 29.5 (continued)

Stage	Action	✓
4. Simultaneous mass treatments and decontamination	Ensure effective, accurate communication of the problem to residents, staff and other stakeholders (Sect. 29.3.5)	
	Conduct initial mass treatments of residents and staff with topical acaricides, where impracticable use oral ivermectin (Sect. 29.3.4). Those with crusted scabies may require both, and more regular treatment than those with normal scabies (Sect. 29.3.4)	
	Where possible decontaminate clothing, bedding and soft furnishings, through laundry or isolation (Sect. 29.3.1, Fig. 29.2)	
	Repeat mass treatments 7 days after initial mass treatments (Sect. 29.3.4)	
	Repeat decontamination of clothing, bedding and soft furnishings in-time with the second mass treatment (Sect. 29.3.1, Fig. 29.2)	
5. After mass treatments	Maintain control measures put in place until outbreak declared over	
	Maintain high index of suspicion about new or remerging cases, and if a case is found repeat actions in step 2 above	
	Manage post-treatment itch	
	Consider setting-up a single prescription-pharmacy supply for the whole institution to provide uniform supply in the case of outbreak re-emergence (Sect. 29.3.3)	
	Declare the outbreak over if no cases found six weeks after second mass treatment (this recommendation is based on our experience in care homes for the elderly, see [6])	
	Ensure effective, accurate communication of the problem to residents, staff and other stakeholders (Sect. 29.3.5)	
	Reassess steps in stage 1 above to reduce future ingress of *S. scabiei* into the institution or transmission within it	

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New Treatment Solutions

30

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Scabies is a contagious disease, and people in the early stage of new infection are often asymptomatic. In addition, mites can survive outside their host in the environment for up to seven days depending on temperature and humidity [1, 2]. Hence, successful scabies management requires the treatment of the infested patient, treatment of subjects with whom the patient had close contact, and elimination of parasites from potentially contaminated clothing and bedding. Over the years, various treatments have been used for scabies, including sulphur compounds (used for centuries), benzyl benzoate (first used in 1931), crotamiton (used since the late 1970s),

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hexachlorocyclohexane (known as gamma benzene hexachloride or lindane, available since 1948), malathion (used since the mid-1970s), permethrin (licensed in 1985) and ivermectin (first used in the 1980s) [3]. A number of herbal remedies have also been used against scabies [4]. The therapeutic arsenal for the management of scabies has considerably increased in the 1970–1980 s, when ivermectin was discovered [5]. Ivermectin is one of the most important drugs to treat scabies nowadays, and its discovery 35 years ago was recently awarded with the 2015 Nobel Prize for Physiology and Medicine [6]. All current scabies treatments have limitations, which will be discussed in this chapter. Mainly, they are poorly effective against the eggs [7, 8], and single target drugs are prone to inducing resistance in the parasite [9–11]. An ideal alternative would be a single-dose regimen drug that kills all developmental stages, including eggs by interfering with multiple target molecules in the parasite.

Optimising existing drugs [12] or repurposing drugs used in the veterinary field have been proposed [13]. Promising few of the latter drug candidates have been experimentally tested in a porcine scabies model. In the future, further advances in functional genomics, combined with target validation through biochemical research, will assist in identifying new drugs [14].

30.1 Limitations of Current Treatments for Scabies

S. scabiei is an obligate parasite and relies on the host epidermis for its nourishment, reproduction, habitat and survival. There are no free-living development stages and no intermediate hosts in its simple life-cycle. This offers an ideal opportunity to target all developmental stages with only one treatment. A few treatments are available for human scabies, which can be divided into topical and oral agents. They are described in Chap. 24.The choice between treatments is mostly based on the age of the patient, the physiological status of the patient (e.g. being pregnant or breastfeeding, or having underlying health issues), the presence and extent of eczematisation or superinfection of the skin, the potential toxicity of the drug either locally or systemically, the cost and availability. Based on their efficacy and safety profiles, topical 5% permethrin and oral ivermectin have become the most relevant treatment options for scabies [15]. To assure the cure of the disease, repeat treatments of these drugs are essential. Topical treatments must be applied to all areas of the skin from head-to-toe and left on overnight before washing off. Incorrect application of the topical agent is observed frequently [16]. Although effective, when applied in compliance with the prescribing information, these treatments have limited patient acceptability and compliance, especially with regards to repeat treatments [17, 18]. Dermatitis secondary to the topical agent and poor penetration of the agent into the hyperkeratotic skin or nails are other limitations and complications of topical medications [18]. Treatment failures are observed because drugs are not 100% effective. Seventy-four per cent to 93% clearance has been observed after treatment with good compliance with 5% topical permethrin, and 68%–86% after oral application of ivermectin [15]. Nevertheless, the major limitations of current therapies are the

limited activity of scabicides against eggs [7] and drug half-lives being too short to cover the whole 14-day life-cycle of the parasite. Most scabicides act by affecting the nerve and muscle function of the parasite and they are only active against mobile stages (larva, nymph and adults) and not eggs. This means that a single treatment doesn't completely disrupt the life-cycle, as hatching larvae can rapidly re-establish and exacerbate infection. Further, *Sarcoptes scabiei* is not a blood-sucking parasite and its access to a drug distributed within the blood circulation is expected to be possibly low. In addition, the proliferation and desquamation of skin cells push the mites and eggs away from the basal epidermal layers and away from exposure to systemic drugs in the dermis. Another potential problem in the future with the use of broad-spectrum anti-parasitic drugs is emerging mite resistance to existing drugs. This is becoming a growing concern, especially with the increased use of permethrin and ivermectin for scabies and for other skin diseases such as pediculosis [19] or demodex-caused rosacea. Parasite resistance has been reported of both permethrin [9, 20] and ivermectin [10, 11] but its clinical importance is still a matter of debate (see Chap. 27).

The inability to effectively treat scabies contributes to considerable economic burden and health disparities in endemic regions. Thus, there is an urgent unmet need for improved acaricide agents with greater efficacy and better suited pharmacological properties, to overcome this insidious disease and its morbidity. The importance of finding an efficacious, easy-to-use, cheap drug is a requirement to start Mass Drug Administration programmes in scabies endemic regions [21, 22]. Ideally, new drug candidates should have both ovicidal and miticidal activity. The recent development of an experimental porcine scabies model provides real potential to conduct translational preclinical and pharmacokinetic studies with new drug candidates.

30.2 The Optimisation of Treatment with Established Scabicide Drugs

In order to optimise and improve scabies treatment outcomes without having to develop and trial new drugs, the use of higher doses of ivermectin is an interesting option. During the clinical development of ivermectin for scabies indication, no high-level dose-ranging studies were performed. The dose of 150–200 μg/kg was considered the standard regimen for many years and millions of people presenting with ivermectin-susceptible parasitic diseases were treated with this dose, based on a reasoned but arbitrary decision. Given the relatively short effectiveness of ivermectin and its short plasma and skin half-lives, the dose regimen may be too low. An emerging hypothesis is that ectoparasite infection may need a higher dose of ivermectin to achieve a cure. This idea was first raised for the treatment of head lice infection (pediculosis). The standard dose of oral ivermectin – 200 μg per kg of body weight – was found to be poorly effective at eradicating head lice infection in numerous studies performed in the United States or in Europe [23–25]. Interestingly, the latest study found that the effectiveness increased with a higher dosage. While a

3-day treatment (days 1, 4 and 8) with 200 µg/kg was about 80% effective in eradicating lice, a 3-day treatment with 400 µg/kg was effective at about 95% to 100% [25]. In 2010, a multicentre, cluster-randomised, double-blinded, controlled trial compared oral ivermectin (two doses at 400 µg/kg on days 1 and 8) with 0.5% malathion lotion (applied twice) in difficult-to-treat head lice infestations. Chosidow et al. found that about 95% of patients receiving ivermectin were lice-free at day 15 [26], whereas malathion treatment achieved 85% efficacy. This increased efficacy of ivermectin might have been due to the higher dosage used in the study. Matching interesting findings have been reported for another parasitic infection, namely *Pediculosis pubis* caused by *Phthirus pubis* (Bernigaud et al., unpublished data). Furthermore, an *in vitro* study evaluating the scabicidal efficacy of ivermectin revealed that the concentration required to kill 50% of adult female mites (50% lethal concentration [LC50]) for ivermectin at 24 h was 1.8 µM [23]. In a therapeutic trial performed in the porcine scabies model using the standard dose of 200 µg/kg oral ivermectin [27], the ivermectin levels were not within the *in vitro* susceptibility range suggested by Mounsey et al. [28], as the maximum concentration of ivermectin in skin was measured to reach 0.069 µM [27], which was presumably insufficient to kill all mites. Dose-ranging experimental studies in the pig model are ongoing, to see if increased ivermectin doses will be more effective at controlling scabies infestation [29]. A French randomised controlled trial is in progress, to compare the efficacy of a single oral 400 µg/kg dose of ivermectin to the conventional treatment dose of 200 µg/kg, given orally three times 7 days apart (days 0, 7 and 14). In this trial, treatments are supplemented with topical 5% permethrin on days 0 and 7 and with daily application of an emollient therapy (PHRC 2014 AOM14612; GALECRUSTED, NCT02841215) [30].

The safety profile of higher doses of oral ivermectin has been evaluated and demonstrated in several studies. In a phase I study including 68 adults receiving doses up to 2000 µg/kg (10 times the FDA-approved dose; 12 participants received the highest dose), ivermectin was well tolerated with no indication of associated CNS toxicity. Adverse events were similar to placebo and were not dose-dependent [31]. In another phase I clinical trial, Muñoz et al. reported similar reassuring findings and no severe adverse event in 54 healthy volunteers receiving a fixed single dose of 18 and 36 mg of ivermectin (corresponding to doses up to 700 µg/kg) [32]. Long experience, including mass drug administration programmes, with oral ivermectin as treatment for various parasitic diseases in humans, such as soil-transmitted helminths, lymphatic filariasis and onchocerciasis, has attested to the drug's safety. Recent randomised clinical trials showed good tolerability of ivermectin when administered at higher doses, including a recent meta-analysis [33]. Gardon et al. evaluated doses up to 800 µg/kg in Ghana, given in an annual single dose (172 patients) or every three months (158 patients) to treat onchocerciasis (*Onchocerca volvulus*). They reported a good safety profile and no serious adverse reactions in the groups receiving high doses [34]. Similar results were obtained by Kamgno et al. in Cameroon, who administered a single high dose of 800 µg/kg [35]. Smit et al. [36] evaluated high ivermectin doses as a new vector control tool to reduce malaria transmission and reported in a randomised, double-blind,

placebo-controlled, clinical trial good tolerability of a ivermectin-dose of 300 μg/kg per day for 3 days in 48 patients. A higher dose of 600 μg/kg per day, for 3 days was also administered and well-tolerated in 47 patients. Subjective ocular problems such as transitory blurred vision appeared, but no severe adverse events were reported with these high doses in all studies [37]. Furthermore, in the randomised controlled trial performed in 2010 by Chosidow et al., the dose of 400 μg/kg of oral ivermectin (given on days 1 and 8) was found to be safe in children (median age of 10 years, interquartile range, 7–14) in difficult-to-treat head lice infestations [26].

30.3 The Repurposing of Drugs Used in the Veterinary Field

To optimise and improve the therapeutic arsenal for scabies treatment, the concept of translating existing drugs used in the veterinary clinic to humans is currently investigated. In the veterinary field, treatment of ectoparasites affecting companion animals or livestock has always been considered a more profitable market for industries. Therefore, innovations and drug developments have been made, making the therapeutic arsenal against parasites much bigger in the veterinary than in the human practice.

A treatment that could be given orally, ideally as a single dose would possibly improve patient compliance to treatment and ease treatment surveillance. Drugs absorbed systemically can diffuse within the intercellular fluid to the upper part of the epidermis. Especially drugs with a low molecular weight and with a high lipid solubility, such as macrocyclic lactones or isoxazoline molecules, are thought to reach the outer layers of the epidermis. The observed presence of host IgG antibodies and human haemoglobin in the midgut of mites [38] indicates that mites ingest serum and hence indeed may take up systemically administered drugs. Data have accumulated demonstrating that moxidectin and afoxolaner, both drugs coming from the veterinary clinic, could be genuine candidates for sustainable scabies control in humans.

Moxidectin is a member of the same family as ivermectin, derived from chemical modification of nemadectin, a fermentation product of *Streptomyces cyaneogriseus* [39]. Owing to its high lipophilicity and low susceptibility to transport by ABC transporters, moxidectin is largely distributed to body compartments and tends to accumulate in fat tissue, which acts as a drug reservoir. Moxidectin was described to have the longest period of activity of the macrocyclic lactones family [39]. The drug is rapidly absorbed with a peak in human blood around 3–4 h after administration and then slowly decreases.

The very long plasma half-life ranged from 20 to 35 days [40, 41]. Moxidectin is registered worldwide for several veterinary indications, including internal and external parasites in cattle, sheep, goats, horses, dogs and cats. In humans, moxidectin has been recently developed by the WHO-based Special Programme for Research and Training in Tropical Diseases (WHO/TDR) for the treatment of onchocerciasis [42, 43].Moxidectin has been approved for this indication in June 2018 as a 8 mg per oral single dose in the United States by the Food and Drug Administration

(FDA) in patients aged 12 years and older. With its promising pharmacological profile, i.e., rapid absorption, large distribution and a much longer half-life in plasma and skin than ivermectin, it has been proposed that a single moxidectin dose may cover the entire life-cycle of the scabies parasite from larvae to nymphs, adults and beyond the egg stage through to the next generation of larva.

Another interesting molecule is afoxolaner, a member of the Isoxazoline family. These are insecticides and acaricides of a new chemical class introduced in the 2000s. The isoxazolines family include afoxolaner, fluralaner, sarolaner and lotilaner [44].These drugs have a broad spectrum of insecticidal and acaricidal activities and are effective against a number of ectoparasites such as fleas, ticks and mites [44, 45]. So far, the available products have been introduced for oral (all drugs) or spot-on (fluralaner) administration in dogs (all drugs) and cats (fluralaner and lotilaner) [46, 47]. Isoxazolines have advantages in terms of pharmacokinetics. After oral intake, isoxazolines are rapidly absorbed in around 2–6 h. They have remarkably long plasma half-lives of around 15 days [47, 48]. Fluralaner could be quantified in plasma (> 10 ng/mL) for up to 112 days after a single oral administration [48]. Isoxazolines are small, lipophilic and unionised molecules and have a high affinity to plasma proteins (> 99%). Laboratory and field studies looking at the efficacy of afoxolaner [49], fluralaner and sarolaner [50–52] against scabies infection in dogs have been recently completed. These led to the European registration of sarolaner for sarcoptic mange in dogs in 2016. With an increased interest in the development of isoxazoline-derived treatments, this new chemical class could be a promising treatment for parasites affecting humans, including *Sarcoptes scabiei* infection in humans.

Two promising drug candidates, namely moxidectin and afoxolaner have been experimentally tested as single dose oral treatments in an established pig-scabies model (see Chap. 8) [27, 53]. In each study, 12 pigs were randomly assigned to three equal groups. The first groups were treated with oral moxidectin (300 µg/kg once) or oral afoxolaner (2.5 mg/kg once), the second groups received oral ivermectin (200 µg/kg twice) and the third groups no treatment against parasites. Mite count, clinical lesions and pruritus were assessed. The efficacy of moxidectin was 98% at day 7 and 100% at day 14. The efficacy of afoxolaner was 100% at day 8 and day 14. The percentages remained unchanged for another 33 days. The efficacy of ivermectin was significantly lower in both studies. The clinical and pruritus scores decreased in treatment groups and remained stable in the untreated control groups. Following these preclinical studies, a multicentre phase II clinical trial in humans is underway in Australia and France, with the aim to develop moxidectin as a new single-dose treatment for scabies (NCT03905265) [54].

30.4 The Identification of New Drug Candidates Using Biochemical Research

As for many infectious diseases, the exploitation advanced molecular and biochemical technologies will help to design new therapeutic tools. Next-generation drugs are immediately needed and should be tailored to scabies mites. Currently, drug

discovery is far less advanced for mites than it is for insect parasites and helminths. Mining multi-omic databases should focus on extracellular scabies mite molecules that (1) have activity that can be modulated by a drug, (2) are unique and essential to survival or (3) underpin reproductive or disease processes (see Chaps. 5 and 6).

30.5 Potential of Essential Oils in Treating Scabies

Not only are the conventional treatments inferior in targeting the whole parasitic life-cycle of scabies mite, they also do not have antibacterial and antipruritic/anti-inflammatory properties, which could provide considerable therapeutic benefits when treating scabies. Secondary bacterial infections mainly due to *Staphylococcus aureus* and *Streptococcus pyogenes* invasion can potentially cause life-threatening disease; hence, therapies with both scabicidal and bactericidal properties may indeed be beneficial. Essential oils have been traditionally used in treating skin conditions (reviewed in [55, 56]) and have been experimentally proven to work against many infectious agents including parasites, bacteria, virus and fungi [57–59] (reviewed in [60–63])]. In addition, they have anti-inflammatory, anti-pruritic and skin conditioning properties (reviewed in [64]).

Several essential oils have shown promising potential in controlling the scabies mite. Some of them have already been evaluated in therapeutic trials in humans to treat scabies. Tea tree oil with benzyl benzoate was tested in Australia [11] and 2.5% eugenol from ocimum oil in China [65]. At 15%, Goanna tea tree oil and 50 mg/mL tea tree antiseptic cream have shown 100% miticidal activity on *S. scabiei* var. *hominis* within 3 h *in vitro,* displaying comparable *in vitro* efficacy to 250 mg/mL benzyl benzoate, 10 mg/g lindane and 18.7 g/kg ivermectin and better *in vitro* efficacy than the 5% permethrin and neem oil [66]. However, this study has been done on a limited number of mites (8–87 mites per compound), and no egg stages were tested. In addition, antibacterial, anti-inflammatory and antipruritic effects of tea tree oil (reviewed in 60)) could be beneficial in scabies patient management. Scabicidal effects of eugenol based essential oils have been widely tested. Clove oil contains 69% to 89% eugenol and 6% to 20% acetyleugenol, while Nutmeg oil has 46.1% isoeugenol and 27.7% methoxyeugenol. In 0.25 h, 100% mite mortality has been observed *in vitro* with 1.56% and 6.25% clove oil in permethrin sensitive mites (*S. scabiei* var. *suis*) and resistant mites (*S. scabiei* var. *canis)* respectively, while nutmeg oil at 25% only showed 50% mortality in 4 h [67]. Isolated pure compounds, eugenol, acetyleugenol and isoeugenol have shown acaricidal effects comparable to benzyl benzoate on mites, while methyleugenol required 3 times higher concentration and much longer exposure time to achieve comparable effects [67]. Eugenol based osmium cream was used in China to treat scabies along with an antipruritic cream [65]. Application twice daily for three times in every third day of 25 mg/g osmium cream has shown promising effects on clearing the scabies infestation [65].In addition, eugenol has antibacterial and antioxidant properties which has shown antibacterial effects against scabies associated bacterial species, mainly *Staphylococcus* and *Streptococcus* [68, 69]. Eugenol is considered non-toxic when

ingested [70]. However, the median lethal dose (LD50) of methyleugenol in rodents was at about 1 g/kg considered slightly toxic, and a concentration higher than 3 mM was cytotoxic to human oral mucous membrane cells. Clove oil was cytotoxic to human dermal fibroblasts and endothelial cells *in vitro* at 0.03%, indicated by skin irritancy [71].

Lemon oil has been shown effective on *S. scabiei* var. *cuniculi* at 20% *in vitro* and *in vivo* [72] and considered nontoxic to humans at its maximum aromatherapy absorption of 0.31 mL [71]. Scabies infected rabbits were successfully treated with 20% lemon oil once a week for 4 weeks [72]. *Cinnamomum zeylanicum* bark oil at 1.25% has shown better scabicidal effect than ivermectin on *S. scabiei* var. *cuniculi* infected rabbits [73] and was bactericidal to *Staphylococcus aureus* well below the miticidal concentration [74]. Cinnamaldehyde, the main constituent of the cinnamon bark oil (92.4%) [74] is considered moderately toxic on the skin at 450 mg/kg in rodents and has shown skin sensitisation in patch tests in humans [71]. Lippa oil at 20% and camphor oil from *Eucalyptus globulus* have shown greater effects than benzyl benzoate when applied for 5 days [75]. All of the above mentioned essential oils are yet to be tested on their ovicidal activity. In our laboratory *in vitro* tests revealed that 12% Manuka oil was 100% miticidal within 4 h, yet its ovicidal effect within this timeframe was suboptimal (unpublished data).

As most essential oils contain hundreds of components, a next step in this area of research will be to identify the active compounds present in promising candidate oils and to determine miticidal, ovicidal and bactericidal properties of these. From there it may be possible to develop a topical single application treatment against scabies and secondary infections and conduct a high level of evidence randomised clinical trial.

30.6 Conclusions

Scabies prevalence remains high worldwide, and currently available treatments may be not sufficiently effective to control the disease. During the past 20 years, a lot of important work has been completed concerning scabies management. The next 10 years will provide a significant improvement for patients as a range of new drugs are expected to enhance the therapeutic arsenal.

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Integrated Management of Scabies and Other Parasitic Diseases

31

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31.1 Introduction

Scabies is a unique neglected tropical disease (NTD) that it is found worldwide across high-, middle-, and low-income countries [1]. However, the greatest disease burden from scabies lies within resource-poor communities [2–5]. In these settings, the transmission of scabies is mainly driven by prolonged skin-to-skin contact from overcrowding [6]. Overcrowding is often associated with poverty, which in turn is associated with poor access to water, sanitation, and hygiene, inadequate housing structures, malnutrition, limited employment, and schooling opportunities, among other suboptimal conditions—risk factors for scabies and also for a variety of other parasitic diseases. Not surprisingly, scabies is coprevalent with other parasitic infections and ectoparasitic infestations, many of which are also NTDs [7–10]. As with other NTDs, scabies impacts the health and well-being of not just individuals, but also families and communities.

Given the accessibility of skin and its relevance to numerous NTDs, many have argued for integrated diagnosis, management, and control of NTDs through the common pathway of skin and its diseases [11–14]. As both a skin disease and a parasitic disease that can be treated with ivermectin, scabies serves as a model for implementing this integration. In this chapter, the rationale and opportunities for integration of scabies control with other NTD programs will be discussed.

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31.2 Scabies Coprevalence with Other Parasitic Diseases

Scabies impacts resource-limited communities burdened with other parasitic diseases, such as ectoparasites and helminths, and polyparasitism is common. For example, lice coprevalence has been documented in urban slums [15, 16] and an isolated fishing village [16] of Brazil, refugees and migrants [17, 18], and homeless populations [19, 20]. Tungiasis and scabies are coprevalent in rural schoolchildren in Ethiopia and Kenya [21, 22], as well as urban slums in Brazil [15]. Scabies is coprevalent with strongyloidiasis in Australian Aboriginal communities [7], soil-transmitted helminths in Zanzibar, Tanzania [8], and lymphatic filariasis in Tanzania [8, 9]. In Brazilian urban impoverished communities, intestinal helminthiases, scabies, and other ectoparasitic skin diseases coexist [10].

31.3 Impact of Scabies

Comparing disability-adjusted life years (DALYs) across neglected tropical diseases, the global burden of disease from scabies is substantial, and greater than several other NTDs including onchocerciasis, dengue, and trachoma [23]. The DALY is a metric used to measure disease burden from mortality and morbidity, calculated as the sum of years of life lost due to premature mortality and years lost owing to disability. The broad, population-level impact of scabies is best understood in the context of clinical complications of the infestation, impact on quality of life, and economic consequences. As detailed in Chaps. 11–13, secondary bacterial infections of skin with *Streptococcus pyogenes* (Group A Streptococcus) and *Staphylococcus aureus* are common local sequelae of scabies infestation that can lead to systemic sequelae of sepsis, poststreptococcal glomerulonephritis, and rheumatic heart disease. Like other NTDs, the morbidity from scabies in resource-limited settings and poor communities is particularly devastating, as discussed in Chaps. 12 and 13.

Pruritus and its related sleep disturbance is a major driver of scabies' impact on families and communities. A study in three urban slums in Brazil demonstrated that 36% of study participants complained about intense or severe itching, which decreased to 6.3% 2 weeks after treatment. A similar trend was noted in regards to intense or severe itch-related sleep disturbance [15]. Importantly, in polyparasitized individuals, pruritus and pruritus-related sleep disturbance is driven by scabies rather than other parasitic infections and infestations [15]. Pruritus and pruritus-related sleep disturbance impact attendance and performance in school and work activities [24, 25], which can have long-range effects on the economic productivity of households and communities [26].

Scabies infestation is associated with a negative impact on quality of life [27–30]. In children, quality of life impairment from scabies has been found to be worse than from atopic dermatitis and psoriasis, though data are limited by small sample sizes [28, 29, 31]. Feeling shame or embarrassment is a primary component of impaired quality of life for both adult and children [27, 30], as has been observed in

other stigmatizing skin conditions such as vitiligo [29, 32] and lymphatic filariasis [33]. Social exclusion, teasing, stigmatization at work/in school, and problems with sexual relationships also contribute [27, 30].

31.4 Integration of Scabies into Existing Public Health Platforms

Integration of control programs across multiple NTDs is a priority set by the World Health Organization (WHO). As pertinent to scabies, the WHO has published an Integrated Management of Childhood Illness (IMCI) skin algorithm [34] and a manual for recognizing NTDs through changes on the skin [35]. Adding an additional disease to an existing NTD platform has been done in Haiti, where malaria was added to an existing lymphatic filariasis soil-transmitted helminth transmission assessment survey platform [36]. The lymphatic filariasis soil-transmitted helminth platform had been successfully implemented in Benin, Togo, Burkina Faso, and Sri Lanka [37–39]. For scabies, opportunities for integration exist through mapping, surveillance, and mass drug administration (MDA) activities.

31.4.1 Mapping and Surveillance

Mapping and surveillance components of existing NTD public health programs offer multiple opportunities for the addition of a scabies component. Scabies prevalence and transmission assessments can be easily added to ongoing control and elimination programs for other NTDs. Guidance for how to approach incorporating a scabies component can be drawn from the literature.

Through skin screening studies, the logistical and operational components of performing efficient skin evaluations have been well-described in a variety of settings and offer different approaches depending on the resources available. A school-based study of 343 participants attending one school in Ethiopia utilized a team of a dermatologist with a primary care physician or health officer to perform a complete skin examination (excluding genitals), hair, nails, and oral cavity on each participant [21]. Similar approaches with pairing of a dermatologist with a nondermatologist medical provider/student to conduct a complete skin examination have been used in school-based skin screening studies in Tanzania, Kenya, Ethiopia, Gabon, Ghana, and Rwanda [22, 40–42]. In Timor-Leste, a multischool screening study of 1396 students utilized a limited clinical examination of exposed areas (defined as upper limbs, lower limbs, scalp, face and neck) to specifically identify scabies and impetigo. The exam was conducted by a medical practitioner who had completed specific training in diagnosing scabies, impetigo, and other childhood skin diseases [43]. A larger school-based study of 13,109 participants across 49 schools from 16 villages in Côte d'Ivoire utilized a two-phase skin evaluation approach, whereby nurses performed a clinical examination of the entire skin from scalp to toes and, if there was a skin abnormality noted, then a dermatologist

evaluated the individual [13]. A similar approach was used in a study of infectious skin conditions involving 3261 participants across 3 schools in Uganda [44].

In a community-based study of childhood skin diseases, 1817 children randomly selected in 30 clusters by probability-proportional-to-size sampling in one region of Mali underwent a complete examination of skin, hairs, nails, and mouth by a dermatologist [45]. In a community-based scabies study of three districts of a fishing village in Brazil, a door-to-door survey was conducted and each household individual that spent an average of at least 4 nights per week during the last 3 months was eligible for participation. A skin examination of the entire body, including breasts and genitals (unless participant refused), was conducted by a single study investigator. Children less than 10 years old were examined in the presence of a caretaker [46].

Mapping studies, transmission assessment surveys, and MDA protocols are commonly school-based and/or community-based. This offers abundant opportunities for integration with scabies work. For example, in the aforementioned Côte d'Ivoire study, the first phase of skin evaluation was integrated with a school-based mass albendazole administration program for soil-transmitted helminths [13]. A single-dose of ivermectin can also be easily administered with other single-dose agents, as is occurring with triple-therapy (ivermectin, diethylcarbamazine, albendazole) to accelerate global elimination of lymphatic filariasis [47].

Consensus diagnostic criteria for scabies have been developed to help standardize the diagnosis of scabies in both individual clinical cases and population-based field work [48], with validation studies ongoing. A simplified clinical examination to diagnose scabies has been proposed to facilitate mapping and efficient public health decision-making. As compared to a fully body examination, limited exam of hands, feet, and lower legs approached 90% sensitivity and limited exam of all exposed limbs (defined as upper arm including axilla, lower arm, hand, lower leg starting below the knee, feet) had a sensitivity of 93.2% for detecting scabies [49]. Validation studies of these simplified exams are still needed. To optimize standardization of skin assessments performed in the field, the development of training materials is important and can be modeled after work done for trachoma grading [50]. Use of assessments with minimum passing score can also be utilized, as has been done in a school-based skin screening study specifically evaluating scabies and impetigo [43].

31.4.2 Mass Drug Administration of Ivermectin and Integrated Management

When public health interventions are required due to high prevalence of scabies, mass drug administration (MDA) with ivermectin is supported by data from numerous settings, as detailed in Chaps. 28 and 29. A recent Cochrane review has shown that ivermectin treatment has a similar high efficacy as compared to topical permethrin [51]. The most robust data for MDA ivermectin is from the Skin Health Intervention Fiji Trial (SHIFT) study, a randomized controlled trial in which three scabies-endemic islands in Fiji were randomized to one of three interventions:

MDA ivermectin, MDA permethrin, standard care test-and-treat with permethrin. The baseline and 12 month prevalence of scabies fell from 32.1% to 1.9% in the ivermectin group (relative reduction in prevalence, 94%; 95% confidence interval [CI], 83 to 100), as compared to 41.7% to 15.8% in the permethrin group (relative reduction, 62%; 95% CI, 49 to 75) and 36.6% to 18.8% in the standard care group (relative reduction, 49%; 95% CI, 37 to 60) [52]. Please see Chap. 28 for a more detailed discussion of mass treatment in endemic settings.

Scabies management in high-prevalence settings with MDA ivermectin is simple and given the broad antiparasitic spectrum of this drug, the intervention is already utilized in several NTD preventive chemotherapy and transmission control programs, namely onchocerciasis, lymphatic filariasis, and strongyloidiasis. With MDA ivermectin for scabies, a single dose of ivermectin 200 μg/kg is administered to the entire population and then repeated one to several weeks later in individuals diagnosed with scabies. Ivermectin is typically administered under direct observation. If there is a contraindication to ivermectin or ivermectin is not available, a variety of topical agents can be used instead, as discussed in Chap. 18.

Specific to scabies coprevalence with other parasitic infections and infestations, both selective treatment with ivermectin and MDA ivermectin approaches have been utilized. In a polyparasitized poor fishing village community in Brazil, selective treatment with ivermectin was used, wherein a single dose of ivermectin followed by a repeat dose 10 days later was administered to all individuals from households where at least one individual was found to be infected with at least one intestinal helminth or one ectoparasite species [10]. Where ivermectin was contraindicated, albendazole or mebendazole was used for intestinal helminths and topical deltamethrin for ectoparasites. Prevalence rates of parasitic skin diseases before treatment, 1 month after, and 9 months after treatment were as follows: active pediculosis 16.1%, 1.0%, and 10.3%; scabies 3.8%, 1.0%, and 1.5%; cutaneous larva migrans 0.7%, 0%, and 0%; tungiasis 51.3%, 52.1%, and 31.2%. Prevalence rates of intestinal helminths diseases before treatment, 1 month after, and 9 months after treatment were as follows: hookworm disease 28.5%, 16.4%, and 7.7%; ascariasis 17.1%, 0.4%, and 7.2%; trichuriasis 16.5%, 3.4%, and 9.4%; strongyloidiasis 11.0%, 0.6%, and 0.7%; and hymenolepiasis 0.6%, 0.4%, and 0.5%. In an Aboriginal community in Australia, scabies and strongyloidiasis were cotargeted diseases in an MDA ivermectin intervention, where a single dose of ivermectin was administered at baseline and month 12. If Strongyloides and/or scabies was diagnosed, a repeated dose was administered 10 to 42 days after each dose at baseline and month 12 [7, 53]. Prevalence of Strongyloides seroprevalence declined from 21% at baseline to 5% at month 6 with a sustained reduction at month 12 (34/618, 6%) and then fell to 2% at month 18 [7]. Prevalence of scabies declined from 4% at baseline to 1% at month 6 with a rise in prevalence to 9% at month 12 due to a presumptive crusted scabies case and then fell to 2% at month 18 [53]. These data indicate that months after the intervention, there is still a positive impact.

Since single-dose ivermectin of 200 μg/kg is successfully used for systematic onchocerciasis and lymphatic filariasis preventive chemotherapy and transmission control programs in many countries, there is an opportunity to evaluate off-target

benefits of onchocerciasis control programs and lymphatic filariasis elimination programs as relevant to scabies control. Multiple publications have made note of the ancillary benefit of MDA ivermectin on reducing scabies prevalence and severity [3, 54–56], and several studies have quantified the effect of MDA ivermectin on scabies as an off-target disease. In Zanzibar, Tanzania, records from 50 health centers were examined from 2000, prior to initiation of MDA ivermectin for lymphatic filariasis and 2005, after six rounds of MDA—one round each year, to obtain data on registered cases of scabies and soil-transmitted helminths (STHs). This retrospective study showed a decline in the number of cases of scabies and STHs diagnosed by community health workers. A 68% to 98% decline in scabies was noted to be statistically significant when aggregated at the island- and district level [8]. In another study examining scabies prevalence across eight Tanzanian villages over 4 years, an initial decline in scabies prevalence from 4.4% (95% CI, 3.7–5.4) at baseline to 0.84% (95% CI, 0.51–1.4) after one round of ivermectin MDA was followed by an increase to 2.5% (95% CI, 1.9–3.3) in Year 3 and 2.9% (95% CI, 2.2–3.8) in Year 4. The authors concluded that these data suggest single-dose ivermectin MDA may not be effective for sustained scabies control in settings with scabies prevalence less than 5% [9]. Beyond evaluating disease prevalence, one modeling study suggested that ivermectin MDA through the African Programme for Onchocerciasis Control averted 116,000 DALYs that would otherwise have been attributed to scabies [57].

In onchocerciasis foci of southeast Nigeria, where MDA ivermectin had been ongoing for a decade, adults reported reduction of itch severity and reduction of skin rashes, which the authors hypothesized was due to a decrease in prevalence of scabies and other endemic ectoparasites—though prevalence was not measured in the study [54]. Through ivermectin administered by the African Programme for Onchocerciasis Control or the Global Programme for Elimination of Lymphatic Filariasis between 2000 and 2007 to over 45 million people in Africa, a substantial proportion of the population was hypothesized to benefit from a reduction in scabies prevalence—though this benefit was not quantified due to lack of epidemiologic data [55]. In Brazilian communities where mass ivermectin treatment has been used to reduce ectoparasitic diseases, ivermectin has been called “God’s drug” by community members due to its association with stopping itch due to scabies, killing head lice, and expelling worms from the intestine [3].

More broadly, integration of ivermectin MDA programs with other disease control programs may offer additional opportunities for integrated management, though systematic data for this approach are still scarce. For example, one study assessed the inhibiting effect of ivermectin on the dengue virus inside Aedes vector mosquitoes and found that dengue virus infection rate and viral load in mosquitoes fed with ivermectin were reduced impressively, in addition to a reduced survival rate of mosquitoes [58]. Future studies are needed to evaluate the effectiveness of ivermectin MDA on dengue transmission dynamics.

For malaria control, there is evidence that ivermectin reduces survival of vector mosquitoes and consequently disrupts transmission. This may offer opportunities for integrated disease control programs on subnational and national levels, including increased cost-effectiveness of control measures [59]. A study from Burkina

Faso, Liberia and Senegal has shown that single dose ivermectin MDA for filariasis (alone or in combination with albendazole), at a dose of 150 μg/kg, affected vector mosquito survival rates (reduction by 34%), and vectorial capacity. Consequently, the authors called for integration of malaria and NTD control strategies, utilizing community-directed treatment models for onchocerciasis and lymphatic filariasis [60]. Higher and repeated doses of ivermectin may reach even more impressive results. A recent randomized controlled trial has shown that a high dose ivermectin regimen (300 and 600 μg/kg/day over 3 days), added to an artemisinin-based product as used in malaria MDA programs, reduced mosquito survival considerably [61]. Modeling of the effect of ivermectin on malaria transmission predicted that adding the 3-day ivermectin regimen to malaria control programs would enhance reduction of malaria prevalence by an additional 56% (600 μg) and 44% (300 μg) in low prevalence areas, and 61% (600 μg) and 54% (300 μg) in high prevalence areas, respectively [61]. Ivermectin was well-tolerated at these dosages. Systematic studies are needed to evaluate the effectiveness of varying ivermectin MDA regimens in different epidemiological, socio-cultural, and ecological settings.

31.4.3 Barriers, Facilitators, and Future Directions

One Health approaches are needed, considering the four different determinant groups linked to neglected tropical and zoonotic diseases, namely "People and Society," "Governance & Health Systems," "Animal Health," and "Environment & Climate Change" [62]. This integrated approach would ideally include public health professionals, community health workers, nurses, physicians, school teachers, and veterinarians, to address not only clinical, but also environmental issues, factors driving transmission dynamics, socio-cultural factors, and access to the health system, to achieve control of a variety of diseases, including zoonotic diseases [62, 63].

In working toward implementation of an integrated approach to public health interventions for scabies and other parasitic diseases, several operational research questions remain unanswered. MDA ivermectin programs that target scabies include a second single dose of ivermectin 200 μg/kg 7–14 days after the first dose to kill newly hatched mites. This second dose is not part of MDA ivermectin for onchocerciasis or lymphatic filariasis. Systematic studies are needed to assess the impact of the second dose of ivermectin for achieving and maintaining scabies control (and of other NTDs), as well as how often MDA ivermectin needs to be administered to maintain long-term scabies control. The appropriate number of ivermectin doses and frequency of MDA may vary depending on the setting (e.g., endemic vs. epidemic, closed vs. open communities, resource-poor vs. resource-rich). MDA approaches with the new oral agents highlighted in Chap. 30 may also differ from an ivermectin MDA approach, particularly if the agent has long-lasting efficacy with a single dose. The development of an effective vaccine against scabies could also change the landscape of scabies control [64].

Practically speaking, there are several barriers related to ivermectin. First, ivermectin is approved for the treatment of scabies in some countries, but notably not

FDA-approved in the United States for scabies. In multiple countries, ivermectin is not approved for use in humans for any indication. Second, ivermectin is not administered to individuals with an allergy to ivermectin, women who are pregnant or breastfeeding within 7 days of delivery, and young children (<5 years old or < 15 kg). While ivermectin is generally believed to be safe and efficacious in pregnant women and young children, there is still insufficient data to recommend its use in these populations [65, 66], which are both high-risk groups for scabies in endemic settings. Furthermore, the MSD (Merck & Co., Inc., Kenilworth, N.J., U.S.A) Mectizan® donation program generously subsidizes ivermectin for qualifying countries based on specific disease targets; scabies is not one of these diseases. Therefore, obtaining ivermectin or an alternative oral agent at an affordable price point remains of tantamount importance for high-prevalent scabies settings, including those that do not continue to participate in the Mectizan® donation program because their disease targets have been met. The same holds true for obtaining effective topical agents for individuals in which ivermectin or an alternative oral agent is contraindicated.

Integrated management of multiple diseases is generally more cost-effective, but requires dismantling existing silo thinking and boundaries between different professional groups, control programs, and funding bodies. Aside from addressing the aforementioned barriers, several potential facilitators of scabies integration into other NTD programs include development of guidelines for initiation and implementation of public health interventions for scabies and a shift from disease-specific vertical programs to disease-integrated horizontal programs that necessitates changes to administrative processes [67, 68]. Implementation research using both qualitative and quantitative study design approaches will be able to identify bottlenecks and optimal implementation measures in a specific setting, by applying research findings into policy and practice, eventually leading to the evidence-based update of guidelines [62, 69]. To varying degrees, several countries have made progress toward integrating NTD training, service delivery, and financial planning [67, 70, 71].

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