

Severe Scabies: A French Multi-centre Study Involving 95 Patients with Crusted and Profuse Disease and Review of the Literature

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The aim of this multi-centre French retrospective study was to identify severe, i.e. crusted and profuse, scabies patients. Records were retrieved from 22 Dermatology or Infectious Diseases departments in the Ile-de-France from January 2009 to January 2015 to characterize epidemiology, demography, diagnosis, contributing factors, treatment features, and outcomes in severe scabies. A total of 95 inpatients (57 crusted and 38 profuse) were included. A higher number of cases was observed among elderly patients (>75 years), mostly living in institutions. Thirteen patients (13.6%) reported a history of previously treated scabies. Sixty-three patients (66.3%) had been seen by a previous practitioner for the current episode (up to 8 previous visits). Initial misdiagnosis (e.g. eczema, prurigo, drug-related eruptions, psoriasis) was documented in 41 patients (43.1%). Fifty-eight patients (61%) had already received 1 or more previous treatments for their current episode. Forty percent received corticosteroids or acitretin for an initial diagnosis of eczema or psoriasis. Median time from the onset of symptoms to the diagnosis of severe scabies was 3 months (range 0.3–22). Itch was present in all patients at diagnosis. Most patients (n=84, 88.4%) had comorbidities. Diagnostic and therapeutic approaches varied. Complications occurred in 11.5% of cases. To date, there is no consensus for diagnosis and treatment, and future standardization of is required for optimal management.

Key words: scabies; *Sarcoptes scabiei*; parasitic; crusted scabies; pruritus; ivermectin; permethrin.

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SIGNIFICANCE

Only a few case series regarding severe scabies have been published, with none from Europe. This multicentric retrospective study on 95 patients in the Ile-de-France characterized the epidemiology, demography, diagnosis, contributing factors, treatments, and outcomes of patients with scabies. Most patients were elderly, vulnerable, had comorbidities, and lived in institutions. Cases were commonly misdiagnosed. Unexpectedly, all patients reported pruritus. Time to diagnosis was long, and complications were not rare, with 3.1% mortality. These results highlight the importance of educating general physicians, specialists, and the general public on these entities and developing standardized treatments to control spreading of this highly contagious disease.

Scabies is a contagious parasitic skin disease caused by *Sarcoptes scabiei* var *hominis* (1–3). It is now regarded as being of sufficient public-health importance because of more frequent outbreaks and a recognition of the longer term health impacts and downstream effects of scabies infestations. Scabies was added to the World Health Organization (WHO) list of neglected tropical diseases in 2017 (4). Severe forms of scabies include crusted and profuse scabies (2). Although there is no prevalence data on severe scabies, there are rare, yet very easily transmissible, forms, with the number of infesting mites reaching several millions (5, 6). Limited case series exist in the literature, and optimal diagnosis and treatment are still missing (7–11). There are no recent data on the characteristics of crusted scabies in Europe. A multicentric retrospective cohort study was conducted on 95 patients with severe scabies in the Ile-de-France (constituting Paris and its area, a north-east region of France).

METHODS

Study setting and period

All Dermatology and Infectious Diseases departments in Ile-de-France, were solicited. To identify cases of severe scabies, the study searched all inpatients recorded over a 6 years-period (1 January 2009 to 1 January 2015) with the diagnosis of "scabies" in the national hospital discharge database (Programme de Médicalisation des Systèmes d'Information; PMSI) using the International Classification of Diseases, 10th Revision ("B86" code). Then, 3 authors (MA, CG, CB) retrospectively reviewed medical records, and only crusted and profuse scabies were included.

Study population, inclusion and exclusion diagnosis criteria

Crusted or profuse scabies were considered as "severe scabies". Scabies diagnosis was performed at 2 different levels: (i) confirmed diagnosis; or (ii) suspected clinical diagnosis. A confirmed diagnosis was a compatible clinical presentation (see below) associated with at least 1 positive investigation (skin scraping, dermoscopic, or histological). Cases without paraclinical confirmation were discussed for inclusion with study investigators expert in the disease (MA, CG, CB) after reviewing the records and the images. Common scabies cases, doubtful cases, or cases where the records were uninterpretable or insufficient were excluded.

For the clinical presentation, the patient's body was divided into 9 parts. Scabies was considered profuse when skin lesions extended to the whole body or there was a diffuse eruption involving the trunk, the back, the face, or the scalp. If ≥ 1 hyperkeratotic lesion(s) were reported, crusted scabies was diagnosed. A positive paraclinical examination was a skin scraping demonstrating *Sarcoptes scabiei* mites, eggs or faecal pellets on microscopy, a dermoscopic examination showing the delta sign, or a skin biopsy with mites, eggs or faecal pellets visible in the stratum corneum.

Data collection

Collected data included demographic information, such as sex, age, residence, comorbidities, clinical information including presence/absence of pruritus, morphology and location of skin lesions, and month of admission. Diagnostic characteristics included time to diagnosis and supporting diagnostic investigations; treatment and outcomes were also recorded.

Statistical analyses

Continuous variables were expressed as medians and categorical variables as numbers (percentage) and extreme values. Statistical analyses were performed using SAS v9.0 (SAS Institute Inc., Cary, NC, USA) software (Version 9.0).

Ethics statement

This is a retrospective non-interventional study. According to the Public Health French Law (art L 1121-1-1, art L 1121-1-2), approval from Institutional Review Board was not required. All participants were informed about the use of their medical data in the study, according to local French regulations.

RESULTS

A total of 95 patients were included during the study period (Fig. 1). Severe scabies was more frequent during winter periods (Fig. S1), with 2 spikes noted in October and December.

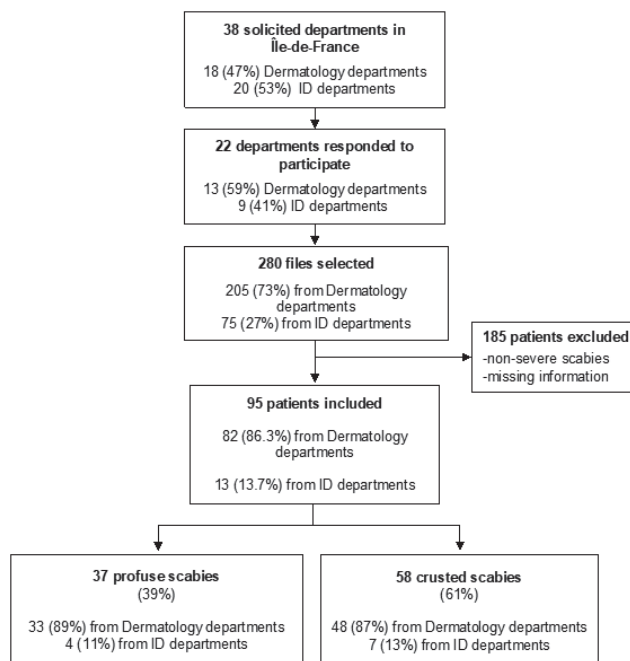


Fig. 1. Study flow chart. ID: infectious diseases.

Demographic characteristics and clinical findings

Of the 95 included patients, 57 (60%) had crusted and 38 (40%) had profuse scabies. characteristics of the patients are shown in Table I. The distribution by age group showed a higher number of patients over 75 years old ($n=30$, 31.5%) (Fig. 2). Fourteen (14.7%) of them lived in institutions, and 16 (16.8%) were homeless.

Thirteen patients (13.6%) reported a history of previously treated scabies (6 confirmed cases (6.3%), and 7 suspicious cases (7.3%)). A case of scabies in close contacts was identified in 35 patients (36.8%), with a

Table I. Demographic, diagnostic, and morbidity/mortality characteristics of all included patients

Characteristics	Number of patients
Total, n (%)	95 (100)
Hospitalized in dermatology department, n (%)	81 (85)
Age, years, median (range)	63 (0.3–97)
Male patients, n (%)	63 (66)
Place of residence, n (%)	
Institution	14 (14.7)
Homeless	16 (16.8)
Delay between symptom onset and diagnosis, months, median (range)	3 (0.3–22)
Hospitalization duration, days, median (range)	12 (1–46)
Error in initial diagnosis, n (%)	41 (43)
Presence of itch, n (%)	95 (100)
Contact case, n (%)	35 (36.8)
Confirmed	10 (10.5)
Suspicious	25 (26.3)
Diagnosis confirmation, n (%)	
Only clinical	18 (18.9)
Parasitological examination	64 (67.3)
Dermoscopic examination	10 (10.5)
Histology	3 (3.1)
Hypereosinophilia, n (%)	47 (49.4)
Complications, n (%)	11 (11.5)
Bacterial infection	8 (8.4)
Death	3 (3.1)

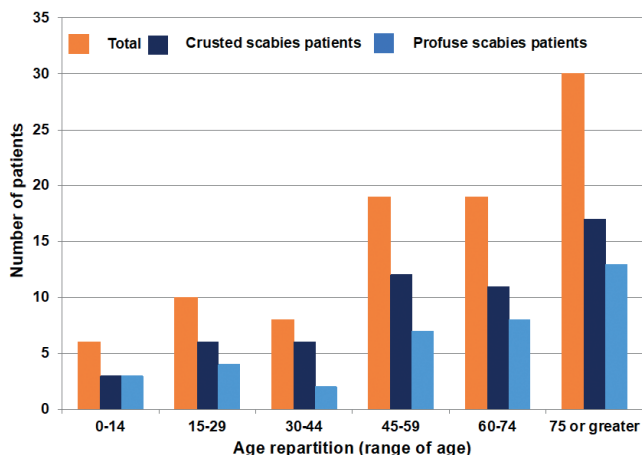


Fig. 2. Age repartition of the study population.

confirmed diagnosis in 10 patients (10.5%) and a suspicious diagnosis in 25 (26.3%) (Table I). Sixty-three patients (66.3%) had been seen by a general practitioner or a specialist for the current episode, at least once, with an extreme of up to 8 previous visits. Initial misdiagnosis was documented in 41 patients (43.1%) (Table I). An eczema flare-up was the most frequently reported initial diagnosis in 19 patients. Other misdiagnoses included prurigo, drug-related eruptions, psoriasis, and pediculosis. Fifty-eight patients (61%) had already received 1 or more treatments before their hospitalization. 40% received corticosteroids, of which 28% were topical, and 1 patient received acitretin for an initial diagnosis of psoriasis. The median time from onset of symptoms to the diagnosis of severe scabies was 3 months, (3 weeks to 22 months). Paraclinical confirmation was performed in 81% of cases, with skin scraping being the most commonly performed test (Table I).

Pruritus was present in all patients at diagnosis and was diffuse in 95% of cases. Burrows were detected in 40% of patients with crusted scabies and in 43% of patients with profuse scabies. Papules, nodules, and vesicles were found in 76%, 10%, and 40% of patients with crusted scabies, respectively. They were found in 84%, 22%, and 57% of patients with profuse scabies, respectively. The distribution of hyperkeratotic lesions in patients with crusted scabies is shown in Fig. 3. Hands were the most commonly affected part (66%). Half of all patients (49.5%) had hypereosinophilia $> 500/\text{mm}^3$ (Table I).

Most patients ($n = 84$, 88.4%) had comorbidities. Sixty patients (63.1%) received immunosuppressive drugs, such as anticancer chemotherapies, azathioprine, mycophenolate mofetil, methotrexate, or rituximab. Corticosteroids were the most common ($n = 53$, 55.7%), especially topical corticosteroids ($n = 40$, 42.1%). Other comorbidities were also commonly associated with severe scabies: 30 patients (31.5%) had neurological disorders, 23 (24.2%) had a history of chronic alcoholism, 13 (13.6%) had diabetes, 12 (12.6%) had an underlying

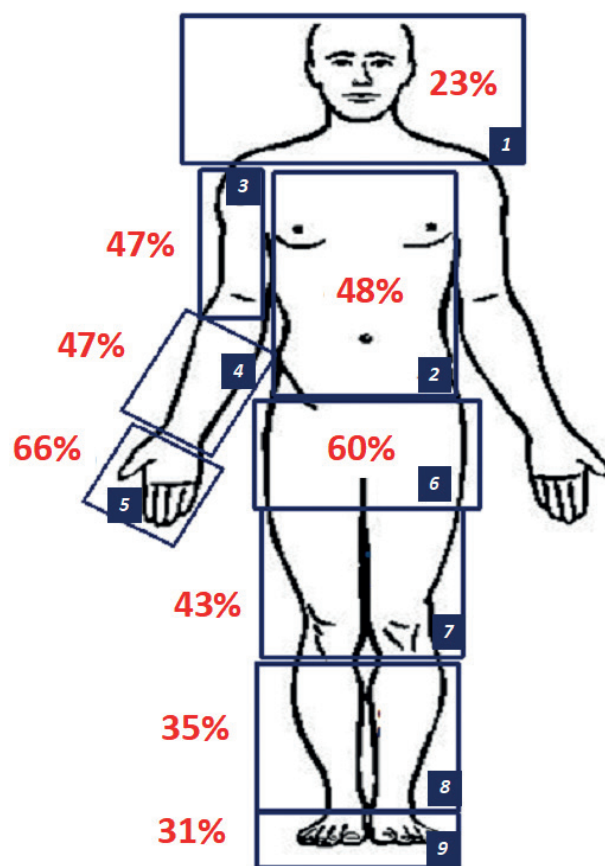


Fig. 3. Distribution of hyperkeratosis in patients with crusted scabies.

1: head: neck: and shoulders; 2: trunk; 3: axilla: arms: and elbows; 4: forearms and wrists; 5: hands; 6: pubis: genitals: and buttocks; 7: thigh and knees; 8: legs and ankles; 9: feet.

skin disease, 11 (11.5%) had psychiatric conditions, and 7 (7.4%) had chronic liver disease.

Therapeutic management, disease course and mortality

A total of 87 patients (91.6%) received a combination of systemic treatment (oral ivermectin 200 $\mu\text{g}/\text{kg}/\text{dose}$) and topical treatment (Table I). The others were treated with oral ivermectin only ($n = 6$, 6.3%) or a topical treatment ($n = 2$, 2.1%). Benzyl benzoate 10% combined with monosulfiram was the most prescribed topical treatment ($n = 63$, 66.3%), followed by 10% benzyl benzoate alone ($n = 17$, 17.9%). The median number of topical applications was 3 [range 1–19], with 1 application per day. In 45 cases (47.4%), ivermectin was prescribed orally in 2 doses of 200 $\mu\text{g}/\text{kg}/\text{dose}$; 31 patients (32.6%) received 3 doses, and 4 patients (4.2%) received 4 doses. The interval between ivermectin doses also varied from 7 days in 45 patients (47.4%), to 15 days in 19 patients (20%). Tolerance of topical treatments was variable, with 22 patients (23.2%) requiring topical corticosteroids applications for eczematization or irritation of their skin. Treatment of contact cases and environmental decontamination were reported in 58.9%.

Median hospitalization duration was 12 days [1–46]. Eleven patients (11.5%) had a complication related to their scabies episode. The most common was secondary infection, mostly bacterial skin infection in 8 patients (8.4%), involving *Staphylococcus aureus* in most cases. Other infections involved *Streptococcus pyogenes* (e.g. Erysipelas, sepsis) and *Escherichia coli* (e.g. sepsis). Four patients with confirmed crusted scabies developed bullous diseases, 3 of which were bullous pemphigoid, and 2 patients developed vasculitis. Three patients with crusted scabies died during their hospitalization (mortality rate of 3.1%) (Table I). The cause of death of the first was acute renal failure and hyperkalaemia; the second had severe hypoglycaemia with loss of consciousness; the third was bedridden and died from *E.coli* and *Staphylococcus aureus* sepsis.

DISCUSSION

This multi-centric regional retrospective study with 95 patients is among the largest case series of severe scabies. Only 5 series are found in the literature (5–9). The current study confirms the long delay in the diagnosis of severe scabies, lasting up to several months, especially in crusted scabies (extreme of 22 months). De Sainte Marie et al. (12) described a mean delay in diagnosis of 4 months (extreme of 13 months) in a series of 31 patients with scabies (mostly common scabies). In the series of crusted scabies by Yélamos et al. (9), the delay was also long, with a median of 7 months and an extreme of up to 16 months. The delayed diagnosis may be explained by a lack of specific clinical signs for severe scabies and insufficient knowledge of the clinical presentation by physicians (9–11). The 2020 International Alliance for the Control of Scabies has facilitated the standardization of common scabies diagnosis (13). However, no diagnostic criteria for severe scabies have been established.

In the current study, severe scabies was more frequent during winter periods. Studies from Scotland and Israel demonstrated higher rates during cooler seasons, possibly related to increased human personal contact and overcrowding, as well as increased mite fertility and survival in cold weather (14).

Half of the patients in the current study were subject to initial misdiagnosis. A majority of them were initially diagnosed with eczema. The other most common differential diagnoses include psoriasis, and adverse drug reaction (15–26). The onset of pruritus and/or skin lesions in the patient's relatives or failure to respond to the first treatment led to the diagnosis in most cases. Misdiagnosis is associated with 2 serious consequences. First, patients with an undiagnosed condition may infest several contacts, as severe scabies are highly contagious. For example, 16 million mites were quantified using *in vivo* confocal microscopy on a crusted scabies skin and thousands of live mites were found in scales collected in

bed sheets of patients with severe scabies (3, 27). In institutions and residential homes, this leads to prolonged and difficult-to-control outbreaks, requiring considerable resources to be managed (28–32). Thus, accurate diagnosis allows disease control. Moreover, misdiagnosis can lead to incorrect prescriptions of treatments (mainly topical corticosteroids), initially improving pruritus, but finally aggravating the infestation, which might cause profuse or crusted scabies and life-threatening complications. A late diagnosis or an inappropriate treatment increases the risk of secondary infection with *Staphylococcus aureus* or *Streptococcus pyogenes*. Specific scabies mite proteins act as inhibitors on all 3 complement pathways, inhibiting host innate immunity (33–38), fostering the growth of bacteria. Previous case reports and series highlighted the misuse of topical corticosteroids (39–48), but no epidemiological studies were able to prove causality. In the current study, more than half of the patients received immunosuppressive drugs and more than 40% had applied topical corticosteroids. Topical corticosteroids alter the skin immune system by reducing or even suppressing local cell-mediated immune responses, resulting in a failure of the host to control the proliferation of mites in the skin. In a porcine model, systemic corticosteroids (oral dexamethasone 0.2 mg/kg/day) increased intensity and duration of infestation with *Sarcoptes scabiei* (49). Pigs treated with corticosteroids develop severe scabies especially crusted scabies, unlike non-treated pigs (50).

Most patients in the series by Roberts et al. (7), Davis et al. (8), and Hasan et al. (11) (97%, 100%, 95% of patients respectively) belonged to Australian indigenous communities. These populations seem to develop severe scabies without known triggering factors. A genetic predisposition that is currently unknown can be the cause. As in the current series, patients in the study by Davis et al. ($n=49$) were mainly males (59%) (8). Yélamos et al. (9) reported a median age of 73 years among their 4 patients, whereas the 3 Australian studies reported younger patients with a median age of 44 years (7, 8, 10). In the current study, the median age was 63 years with a majority of elderly patients over 75 years old. The majority of patients in our retrospective study cohort had comorbidities (89%), which is consistent with the other series (7–11).

Contrary to what has been reported in the literature suggesting crusted scabies is not itchy (24, 51–55), all patients in the current study complained of itch, at time of diagnosis. Complications included secondary bacterial infection, electrolyte imbalance, and erythroderma (24). Patients with severe scabies are also at higher risk of developing vasculitis (56–63) and bullous pemphigoid (64), which were seen in 2% and 4% of our patients, respectively. It is assumed that the mites' antigens could share similarities with those of the dermo-epidermal junction leading to antibody production against proteins of the dermo-epidermal junction (65). The complications

of severe scabies make the mortality of this entity non-negligible. In the current series, 3 patients died (3.1%). Roberts et al. and Hasan et al. reported a higher mortality of 14% (4) and 16%, respectively (9). While scabies is often considered as a benign infection, it can become a serious condition when not well-controlled (66–68).

Treatment of severe scabies is long, often requiring a prolonged hospital stay. Different treatment protocols were used in the current study, testifying a lack of standardization: topical treatments were associated or not with oral ivermectin, and different numbers of applications and dosing intervals were used. The majority of patients were treated with oral ivermectin (200 µg/kg/dose) and 10% benzoyl benzoate + 2% monosulfiram. On the one hand, topical treatments differed because of lack of consensus on the treatment, and, on the other hand, because availabilities of topical treatments have changed during the study period. Ten percent benzyl benzoate with 2% sulfiram was out of stock from November 2012, then replaced by an imported product (10% benzyl benzoate alone) from Germany in February 2013. A French commercial product then became available in October 2015 (also with 10% benzyl benzoate only). Esdepallethrin with piperonyl butoxide was used as an alternative, which was withdrawn from the French market in July 2017. Permethrin was not available in France until after July 2015. Treatment usually consists of a combination of topical acaricides and systemic ivermectin at repeated doses (69–71). Only a few therapeutic studies for treatment of crusted scabies including more than 5 patients exist in the literature (summarized in **Table II**) (6, 8, 11, 72, 73). A Cochrane review for the treatment of scabies does not mention severe scabies (74). The recent development of a porcine model holds a significant potential for developing scabies treatment (75–77), in addition to the development of randomized controlled clinical trials, such as the one granted in France by the French Ministry of Health, comparing the efficacy of ivermectin given orally at a dose of 400 µg/kg vs the conventional treatment dose of 200 µg/kg, 3 times 7 days apart (on

D0, D7, and D14), with application in both arms of daily emollient therapy and topical 5% permethrin on D0 and D7 (GALECRUSTED, NCT02841215) (78).

Although the current study is among the largest retrospective study on severe scabies, it has some limitations. Besides its retrospective nature, it includes only hospitalized patients, who are usually older patients with comorbidities. Moreover, not all cases were confirmed by a paraclinical examination, although all clinically-confirmed cases were reviewed by experts in scabies. Management was based on French practice, noting the unavailability of topical treatments such as permethrin during the studied period. The current study did not evaluate the efficacy of the treatments, because this was not the objective of the study. Ongoing clinical trials for optimal treatments in crusted scabies will give a better highlight on the preferred therapeutic modalities.

Conclusion

Severe cases of scabies hospitalized in the French Parisian area were mostly seen in elderly, immunosuppressed people with comorbidities who live in residential institutions. Clinical presentation might lead to misdiagnosis in many cases. Contrary to what has been reported in the literature about crusted scabies causing no or less itch, all patients in the current study reported itch, at time of diagnosis. Severe forms of scabies are often misdiagnosed with eczema, and previous treatments with topical corticosteroids may increase complications. To date, there is no consensus on the clinical management of these cases. Standardization of the diagnosis and treatment is essential, and educating general physicians and geriatricians about these entities is indispensable for optimizing management.

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Conflicts of interest: CB acts as unpaid scientific advisor for Medicines Development for Global Health. OC received fees for an advisory board meeting, he is the PI of phase 2 moxidectin RCT supported by Medicines Development for Global Health. No other competing interests were declared.

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Table II. Therapeutic studies in the literature including more than 5 patients with crusted scabies

Author(s)	Year	Treatment studied	Results	Patients <i>n</i>
Hasan et al. (11)	2020	Ivermectin 200 µg/kg/dose 3–7 doses (median 5, ranges 0–13)	71% efficacy	92
Davis (8)	2013	Ivermectin 200 µg/kg/dose 2–10 doses 47 patients: + benzyl benzoate + tea tree oil 2 patients: + permethrin 5%	100% efficacy	49
Nofal (72)	2009	Ivermectin 200 µg/kg/dose Day 10 ± day 14 ± day 28	30% efficacy at day 14 90% at day 28	8
Roberts et al. (7)	2005	Ivermectin 200 µg/kg/dose Days 0, 1, 7, 8, 14, ±21 ±28 + keratolytic treatment	100% efficacy at day 30	78
Dia et al. (73)	1999	Ivermectin 200 µg/kg/dose 2 doses	100% efficacy	11

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