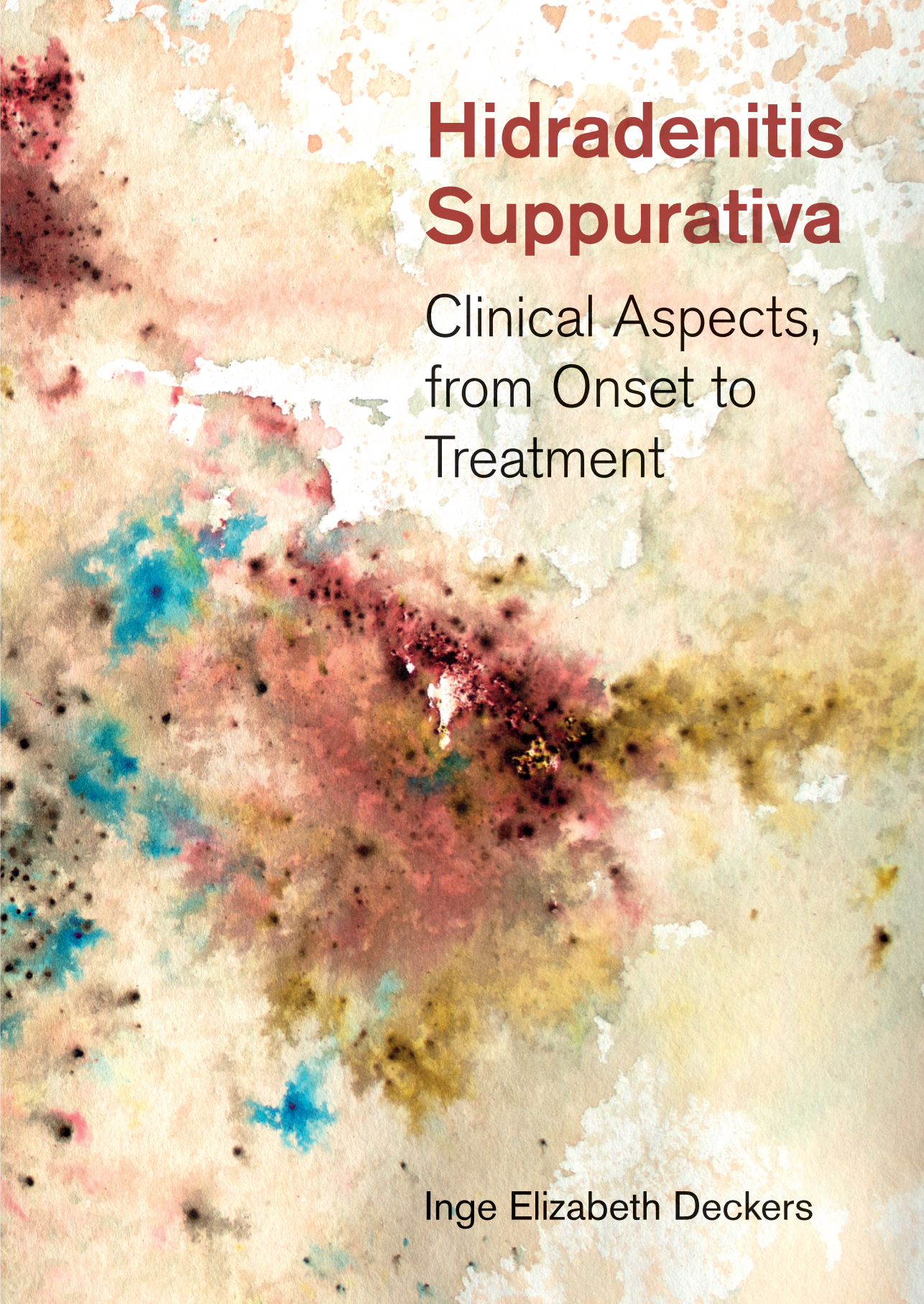

Hidradenitis Suppurativa
Clinical Aspects, from Onset to Treatment
Inge Elizabeth Deckers

Hidradenitis Suppurativa

Clinical Aspects, from Onset to Treatment

Inge Elizabeth Deckers

Hidradenitis Suppurativa
Clinical Aspects, from Onset to Treatment
Inge Elizabeth Deckers

Colofon

ISBN 978-94-6169-824-7

Cover design by Annelies Bode

Layout and Printing: Optima Grafische Communicatie (www.ogc.nl)

Hidradenitis Suppurativa

Clinical aspects, from onset to treatment

Hidradenitis suppurativa

Klinische aspecten, van ontstaan tot behandeling

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 26 april 2016 om 15:30 uur

door

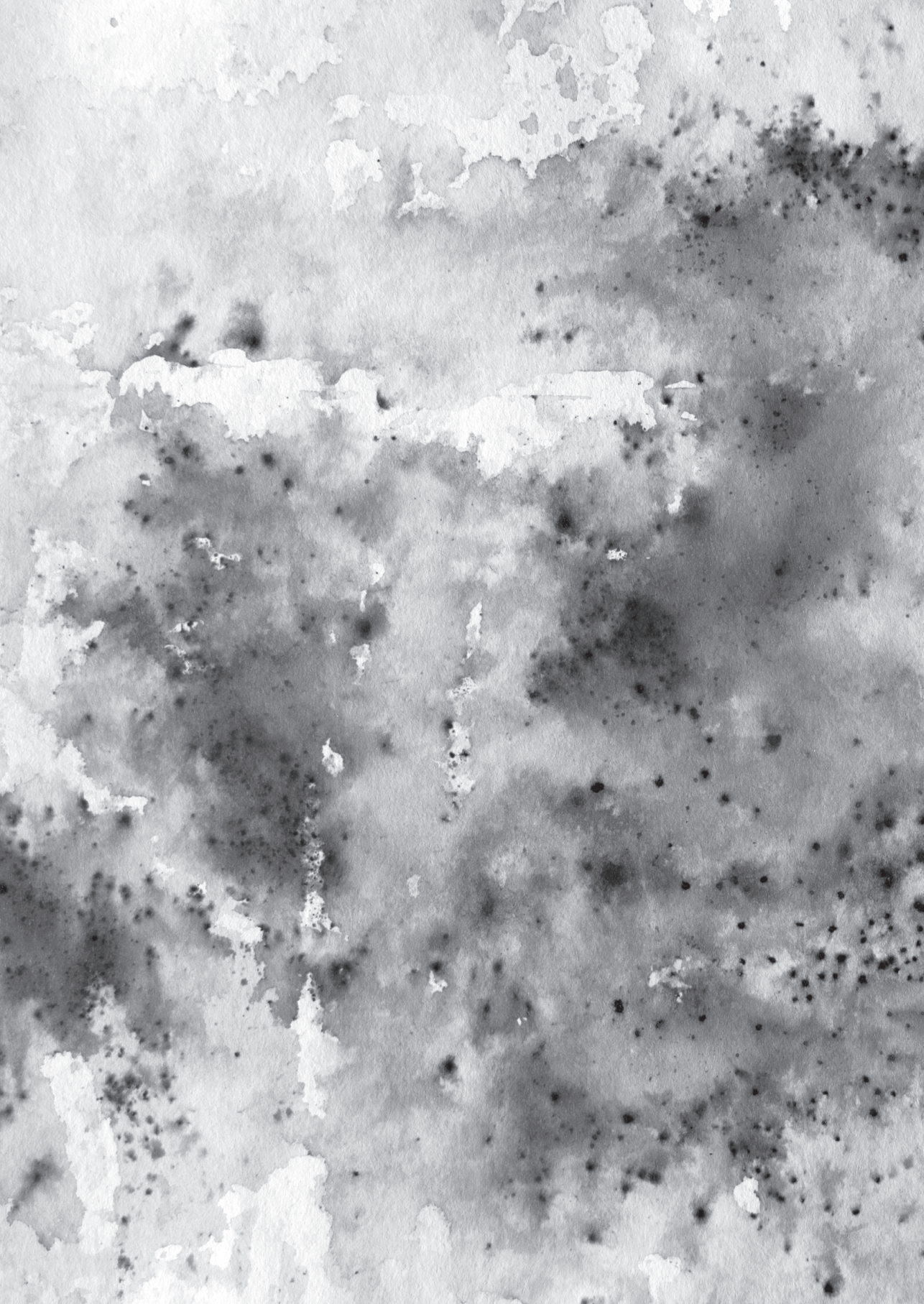
Inge Elizabeth Deckers
geboren te Enschede

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor:	Prof.dr. E.P. Prens
Overige leden:	Prof.dr. T.E.C. Nijsten Prof.dr. G.B.E. Jemec Dr. B. Horváth
Copromotoren:	Dr. H.H. van der Zee Dr. J. Boer

CONTENTS



Chapter 1

General introduction and aims of this thesis

Parts of the introduction are published as:

Epidemiology of hidradenitis suppurativa: prevalence, pathogenesis, and factors associated with the development of HS.
Inge E. Deckers, Hessel H. van der Zee, Errol P. Prens

Curr Derm Rep 2014;3:54-60

The handicap of hidradenitis suppurativa.
Inge E. Deckers, Alexa B. Kimball

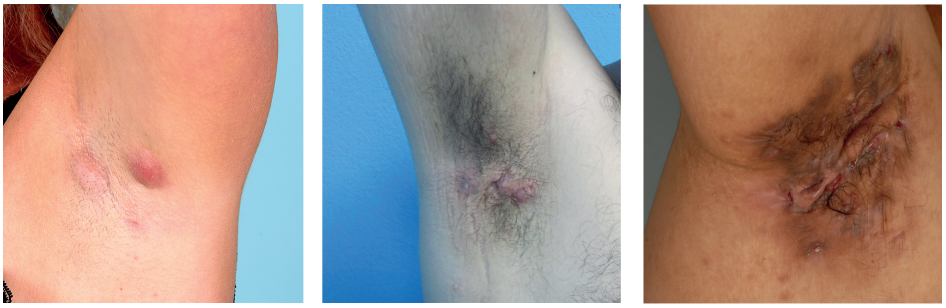
Dermatol Clin 2016;34:17-22

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease. Patients present with painful deep-seated inflammatory nodules or abscesses, mainly located in the inverse body areas such as the axillae and groin.[1,2] The name hidradenitis suppurativa is derived from the Greek words hidros (sweat), aden (glands) and itis (inflammation) and the Latin word suppurativa (pus-forming). The disease was first described by the French surgeon Velpeau in the 'Dictionnaire de médicine ou repertoire general des sciences médicales'.[3] In 1864 Verneuil, also a French surgeon, introduced the name 'hidrosadénite phlegmoneuse', because he thought that the abscesses originated from the sweat glands, due to their location in the axillae.[4] Hereafter, the disease was also referred to as Verneuil's disease. However, already in 1902 it was suggested that the sweat glands were not primarily involved in HS.[5] In 1989 HS got his third name; acne inversa, because it was suggested that HS shared similarities with pathogenesis of acne vulgaris.[6,7] However, the sebaceous glands are not primarily involved in HS and common treatments for acne vulgaris showed limited effects in HS.[8–10] Sporadically, the names fox den disease or pyoderma fistulans significa are used to describe a severe subtype of HS.[11,12] In Dutch literature the name acne ectopica is also commonly used, which was introduced in a Dutch text book on Dermatology in 1983.[13] The net effect is that this painful debilitating disease has multiple names, none of which is appropriate. However, for this thesis we chose to remain with hidradenitis suppurativa, because it is still most commonly used in current literature.

1. CLINICAL PRESENTATION

HS is a characterized by painful, inflammatory nodules, sterile abscesses and sinus tract formation, followed by scarring and tissue fibrosis (Figure 1).[1,14] These lesions are located at specific body areas such as the axillary, inguinal, pubic and gluteal area. Less frequently affected body areas are the abdominal, facial, retroauriculair, and the sub- and inframammary areas. The presence of double comedones or pseudo-comedones is typical for HS.[14] Canoui-Poitrine *et al.* suggested that three clinical phenotypes exist.[15] The most common phenotype is the 'axillary-mammary' type, in which mostly the armpits and breasts are involved with hypertrophic scars. The 'follicular' type is characterized by the presence of comedones, papules and folliculitis, located at the armpits and/or breast, but also the ears, chest, back and legs are frequently affected. Patients with the 'gluteal' type show similar lesions as the 'follicular' type; however, in these patients most lesions are located at the gluteal area. Van der Zee and Jemec recently suggested that there are six different types;[16] the regular type, the frictional furuncle type (overweight patients with lesions at friction sites), the scarring folliculitis type (pustules, cysts, cribiform scarring and comedones at the buttocks, inguinal and pubic region), the conglobate

type (mostly in overweight men with cyst formation and acne conglobate on the back and face), the syndromic type (patients with concomitant diseases such as pyoderma gangrenosum and arthritis) and the ectopic type (involvement of the face).[16]



Hurley stadium I | Hurley stadium II | Hurley stadium III

Figure 1. The clinical presentation of hidradenitis suppurativa.

2. EPIDEMIOLOGY

Several studies have attempted to determine the prevalence of HS. In 1996, Jemec *et al.* reported a prevalence of 4% in young adults and 1% in general population.[17] Revuz *et al.* confirmed the prevalence of 1% in 2008, with a questionnaire-based survey among 6,887 subjects.[18] However, recent studies from American populations reported lower prevalences of 0.05% to 0.13%.[19,20] However, these studies might underestimate the prevalence, because patients were only included if they had sought medical care for their disease. Unfortunately, because of embarrassment, patients often postpone seeking medical help.[21]

HS usually develops after puberty with a peak age of onset in the early twenties,[2,22,23] and women are generally more frequently affected than men, with a female-to-male ratio of 3:1.[17,18] Prepubertal onset is thought to be rare, although multiple case reports of children with HS exist.[24,25] HS is a chronic disease; von der Werth and Williams showed that 90% of their studied patients still had an active disease after a disease duration of nearly 19 years.[22] Conversely, it has been said that the prevalence diminishes over time.[14,18,26] Especially the menopause is mentioned as a point in life whereafter women would become free of symptoms.[2] However, the actual percentage of postmenopausal women with active disease is unknown.

3. ETIOLOGY

3.1 Pathogenesis

The pathogenesis of HS is still largely unknown, and is probably multifactorial.[27] Since the last two decades, the primary event is thought to be occlusion of the terminal hair follicle,[28] caused by infundibular hyperkeratosis and hyperplasia of the follicular epithelium.[29,30] This occlusion results in the accumulation of cellular debris, cyst formation, and rupture of the hair follicle, followed by abscess formation, and in later stages, the development of sinus tracts and scarring.[31,32] In unaffected skin of HS patients, a significant reduction of sebaceous glands has been observed in comparison with healthy subjects.[8] The authors hypothesized that the absence of sebum results in higher friction in the infundibulum of the hair follicles, resulting in hyperkeratosis and rupture of the hair follicles. In addition, it was found that all skin samples from HS patients showed perivascular inflammation, perifollicular inflammation, or both.[8] This is remarkable, since the samples were perilesional, from clinically unaffected skin that showed no signs of inflammation or scarring. This would support the hypothesis that an immunological dysregulation is also involved in the development of HS.

Many factors, endogenous as well as exogenous, are associated with the development and maintenance of the disease. Exogenous factors important in the pathogenesis of HS are: smoking, obesity, bacterial superinfections and friction. Endogenous factors include genetic predisposition, aberrant immunity, and hormonal influences.

3.1.1 Smoking

Smoking is a factor that is strongly associated with HS. In multiple studies, high percentages of active smokers (60-90%) or ex-smokers (5-15%) have been reported, and smokers tend to have a more severe disease than nonsmokers.[33–35] Nicotine can be detected in axillary sweat for up to eight days after smoking cigarettes, and the levels of nicotine are significantly higher in apocrine sweat than in eccrine sweat.[36] Since more apocrine sweat glands are located in the intertriginous areas, the concentration of nicotine is higher in the skin of these areas.[36,37] Nicotine promotes inflammatory reactions, like provoking mast cell degranulation, and enhancing the survival and chemotaxis of neutrophils.[38–40] Furthermore, an *in vitro* model has shown that nicotine can induce epidermal hyperplasia and follicular plugging, which is also found in the skin of HS patients.[37,41]

3.1.2 Obesity

Most HS patients (45-80%) are overweight with a body mass index (BMI) above 25 kg/m^2,[23,33] also obesity (BMI > 30 kg/m^2) is associated with a more severe disease.[34] There are multiple explanations why obesity can contribute to the development of HS. First, it is hypothesized that in obese patients, the increased skin-to-skin contact enhances

mechanical friction, which can cause micro-tears of the hair follicles in predisposed individuals.[37] These micro-tears can eventually lead to rupture of the hair follicle and spilling of the follicular content, resulting in inflammation and abscess formation.[8] Second, the overlapping skin folds may cause sweat retention, which can cause irritation and maceration when combined with friction, leading to skin inflammation. Third, bacterial growth is favored by the often humid and warm microclimate present in the skinfolds, causing secondary infections of the inflamed skin.[27,42] Fourth, obese patients have increased levels of circulation pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β and IL-6.[43] These cytokines, especially TNF-α and IL-1β, are also elevated in the skin of HS patients.[44] Therefore, it is conceivable that the enhanced levels of pro-inflammatory cytokines, partly produced by adipocytes,[43] contribute to the development of HS.

3.1.3 Genetic factors

In approximately 40% of the patients, HS occurs in one or more family members.[23,26] In 1985 Fitzsimmons *et al.* suggested that HS follows an autosomal dominant pattern, even though only 34% of the patients had a first degree family member with HS.[45,46] They blamed this low percentage on the high number of family members that were still under the age of 20. In 2000 von der Werth *et al.* re-examined the same families, but still a 50% frequency for an autosomal dominant transmission was not reached.[26] Hereafter, multiple studies were conducted to determine the genetic basis in patients with HS. Even though several genetic loci have been identified that are associated with HS, no causative genes have been found. Mutations in the γ-secretase genes PSENEN, PSEN1 and NCSTN were identified in families with multiple family members suffering from a specific form of HS, in whom not only the normal locations, but also atypical sites were affected.[47–50] However, these mutations could not be confirmed in a larger HS cohort.[47,48] When the function of γ-secretase is disrupted in mice, it results in follicular keratinization, follicular atrophy, the formation of epidermal cysts, absence of sebaceous glands, and epidermal hyperplasia, characteristics that also can be found in HS.[48] But more research is necessary to determine the influence of genetic factors in the pathogenesis of HS.

3.1.4 Aberrant immune response

The chronic inflammatory nature combined with the frequent absence of pathogenic bacteria suggests a role of an aberrant immunity in HS. This suspicion is further supported by the reported co-occurrence with sterile arthritis and Crohn´s disease (CD).[51] Multiple studies have shown that the levels of several inflammatory and anti-inflammatory cytokines are elevated in HS lesions.[44,52–54] Upregulated cytokines in HS lesions include IL-1β, TNF-α, IL-10, IL-11, IL-17A, CXCL9, monokine induced by interferon-γ, and B-lymphocyte chemoattractant. On the other hand, IL-2, IL-4, IL-5 and interferon-γ were

hardly detectable in HS lesions.[44,54,55] The enhanced expression of IL-17A could reflect activation of the IL-23/Th17 pathway in lesional HS skin. It was indeed demonstrated that IL-12 and IL-23 were both abundantly expressed in macrophages in the dermis of HS lesions together with IL-17 producing T cells.[53]

3.1.5 Bacterial infection

For a long time, it was thought that bacterial infection played an imported role in the development of HS. However, bacterial cultures from HS lesions are often sterile or only grow commensal skin flora, such as coagulase-negative staphylococci, *Staphylococcus aureus*, and strains of the intestinal flora e.g. *Escherichia coli*.[56–61] Staphylococcus species were mostly found in Hurley stage I lesions, whereas in Hurley stage II or III more often coagulase-negative staphylococci and a mix group of anaerobic flora were found.[62] This suggests that bacterial colonization is a secondary event and that superinfections may worsen flare ups.[14,37]

3.1.6 Hormonal influences

A relation between HS and hormones seems conceivable since the onset of the disease is mostly after puberty and the prevalence seems to gradually decrease after menopause.[63] In addition, women reported premenstrual flare-ups,[22] and improvement of the disease during pregnancy.[63,64] However, no differences have been found in plasma androgen levels in women with HS and BMI-matched healthy controls.[65,66] Therefore, the role of hormones in the development of HS remains questionable.

3.1.7 External factors

HS patients report a wide range of external factors that may induce lesions.[22] Morgan *et al*. investigated the role of shaving, the use of chemical depilatories, deodorants, and talcum powder as causative factors for HS, and concluded that these factors do not play a role in the initiation of HS.[67] Probably the only external factor that is associated with HS is mechanical friction. Patients report that wearing tight clothes enhanced the number of inflammatory lesions and that wearing loose clothes decreased the symptoms of their HS.[22] In obese patients the abdomen and waist can be more affected due to friction of the waist belt, which can also resolve after weight loss.[68] The role of mechanical friction is further supported by two case reports: a child developed HS-like lesions in a nevus comedonicus after she started moving around,[69] and a man developed HS-like lesions on his leg stump after he started to wear a leg prosthesis.[70]

3.2 Diseases associated with hidradenitis suppurativa

Multiple diseases have been reported to co-occur with HS. Many of these diseases are caused by immunological dysregulation or by a genetic disorder related to the function of the hair follicles.

Since infundibular occlusion has been established as a key pathogenic event, HS has been grouped with three other diseases that result from follicular occlusion, called the follicular occlusion tetrad: acne conglobata, pilonidal cysts and dissecting cellulitis of the scalp.[71–73] It has been recorded that up to 26% of HS patients have a history of severe acne, and up to 30% have a history of pilonidal cysts.[15] However, it can be difficult to differentiate between HS and a pilonidal cyst on a clinical basis.

HS is frequently associated with inflammatory bowel disease (IBD), mostly with CD.[51,74–77] In one study, up to 38% of 61 HS patients were diagnosed with CD,[74] whereas in studies performed in IBD patients the prevalence of HS ranges between 1.2% and 23%.[75,77,78] The clinical presentations of HS and CD can be similar, because both can show perianal abscesses and fistulas, have a clinical course with periods of exacerbation and remission, and show a good response to biologics such as TNF-α inhibitors.[51,79,80] However, it is difficult to differentiate histologically between HS and CD, because in both diseases diffuse tissue inflammation with epithelioid granulomas can be present.[81,82] Also, for HS as well as for CD, smoking is a triggering factor, and is associated with a more severe disease.[79,80]

Recently, HS has been associated with metabolic syndrome. The cluster of cardiovascular risk factors, including diabetes mellitus, hypertension, dyslipidemia and obesity, showed to be more frequently present in patients with HS than in controls.[83–85] A recent systematic review confirmed the association, showing an increased odds ratio of 2.2 for metabolic syndrome in HS.[86] Patients with HS that were referred to a dermatologist, even had an odds ratio of 3.9 for metabolic syndrome.[83] However, it is still under debate if the proinflammatory state of metabolic syndrome is causative to HS, or a secondary effect of HS.[83–85]

More rarely, HS has been associated with pyoderma gangrenosum (PG).[73,87] PG is a rare, chronic, inflammatory skin disease, characterized by progressive ulcers, typically affecting the lower extremities or the trunk, but all body areas can be affected.[88] One study has described eleven HS patients having PG-like ulcers; most of the patients had these ulcers at locations where they also suffered from HS.[87] Therefore, it is possible that these ulcerations were counted as PG, while chronic ulcerations from HS could not be excluded.

Spondyloarthropathy has also been associated with HS, mostly in African-American or Afro-Caribbean men.[73] The peripheral joints were mostly affected, generally in an asymmetric pattern, whereby flare-ups of HS triggered the joint symptoms. Laboratory testing showed that in most patients the rheumatoid factor was negative, and there

was no association with HLA-B27.[89–91] In a recent French study, 24 of the 640 HS patients (3.7%) had spondyloarthritis according to the European Spondylarthropathy Study Group (ESSG) criteria. In total, 43 patients fulfilled the criteria for arthritis, enthesitis and/or inflammatory back pain. In 16 of these patients HLA-B27 was tested, and was positive in seven patients.[92]

4. DIAGNOSIS

The diagnosis of HS is based on the clinical presentation and no diagnostic tests are available to set the diagnosis. The diagnosis has to be established based on the history of the patient and the physical examination. During the international symposium of the Hidradenitis Suppurativa Foundation in March 2009, three criteria have been adopted on which the diagnosis of HS should be made.[93,94] First, typical lesions should be present i.e. deep-seated nodules, abscesses, draining sinuses, fibrosis and/or bridged scars. Second, these lesions should be located at typical localizations such as the axillae, groin, perianal and gluteal area. Finally, the disease course has to be characterized by chronicity and relapses.[2,93,95]

Validated questions have been developed to make the diagnosis through questionnaires.[96] The following three questions showed to have high sensitivity (SE) and specificity (SP):

- Do you repeatedly have outbreaks of big sore or painful nodules or boils that heal with scars in any of these location: Groins, armpits, sexual organs, anal region and under the breasts. (SE: 0.97, SP: 0.82)
- During the last 12 months did you repeatedly have big painful nodules or boils located in the armpits or the groin, a disease called hidradenitis suppurativa? (SE: 0.92, SP: 0.86)
- Have you had at least two outbreaks of boils during the last 6 months? (SE: 0.95, SP: 0.85)

4.1 Severity scores

To date, multiple severity scores have been used to assess disease severity. The Hurley score is the oldest and still most commonly used (Table I and Figure 1).[2,97] Even though it is easy in use; it is very static and therefore less suitable for monitoring treatment efficacy. In 2003 the Sartorius score was introduced which was modified in 2009. It is based on the number of areas involved and the number of nodules, fistulas and hypertrophic scars.[23,98] However, because of its comprehensiveness, it is time consuming, making it less suitable for daily practice. One of the latest severity scores is the 'Hidradenitis Suppurativa Physician Global Assessment' (HS-PGA) score. This five scale score ranges from

Table I. Hurley classification

I	Abscess formation, single or multiple, without sinus tracts and cicatrization
II	Recurrent abscesses with sinus tract formation and cicatrization. Single or multiple, separated lesions
III	Multiple interconnected tracts and abscesses throughout an entire area

Hurley classification for clinical staging of disease severity.[2,97]

clear to very severe, and is based on the number of noninflammatory nodules, inflammatory nodules, abscesses and draining fistulas (Table II). This validated score is easy to use and suitable for observing change during treatment, and therefore frequently used nowadays.[93,99]

However, for all these severity scores it remains questionable to determine when a treatment has a meaningful effect. Therefore the 'Hidradenitis Suppurativa Clinical Response' (HiSCR) has been developed as a clinical endpoint in HS treatments.[100] For this scoring system the number of abscesses, inflammatory nodules and draining fistulas have to be counted. Patients who respond to treatment (achieving HiSCR) should have at least 50% reduction in the total number of abscesses and inflammatory nodules, whereas there should be no increase in the number abscesses or draining fistulas.[100]

Table II. Physician's global assessment scale of hidradenitis suppurativa[a]

Clear	No noninflammatory nodules, inflammatory nodules, draining fistulas or abscesses
Minimal	Only noninflammatory nodules, but no inflammatory nodules, draining fistulas or abscesses.
Mild	Less than five inflammatory nodules, but no abscesses or draining fistulas; **or** one abscess or draining fistula, but no inflammatory nodules
Moderate	Five or more inflammatory nodules, but no abscesses or draining fistulas; **or** one abscess or draining fistula and at least one inflammatory nodule; **or** two to five abscesses or draining fistulas and less than ten inflammatory nodules
Severe	Two to five abscesses or draining fistulas and more than ten inflammatory nodules
Very severe	More than five abscesses or draining fistulas

[a] Adjusted physician's global assessment scale for hidradenitis suppurativa.[93,99]

5. THE IMPACT OF HIDRADENITIS SUPPURATIVA

5.1 Quality of life

HS can have a profound influence on quality of life (QoL). Owing to pain, patients are unable to perform their everyday tasks, go to work or enjoy sports. In addition, patients often feel embarrassed because of the malodorous suppurative discharge and often hide the disease even from close relatives.[101] Mostly the Dermatology Life Quality Index (DLQI) and the Skindex-29 are used to assess QoL in dermatological patients. For both, a higher score implies a greater impact on QoL. All studies performed on QoL in patients

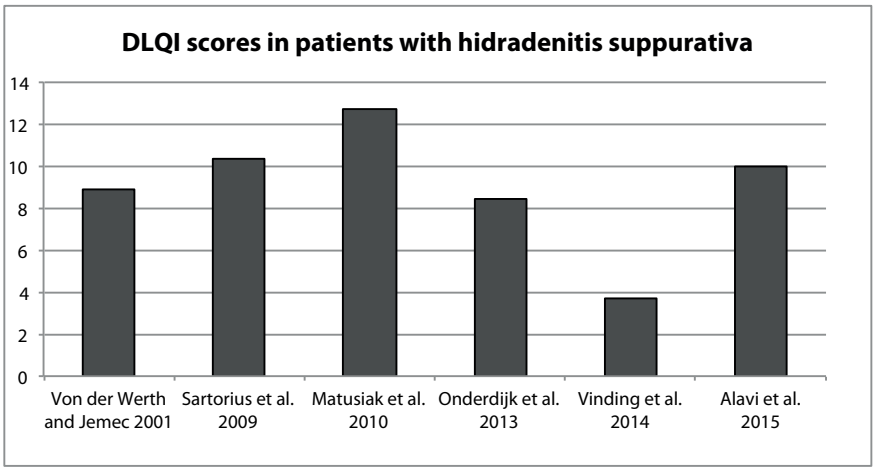


Figure 2. Overview of the Dermatological Life Quality Index (DLQI) scores in patients with hidradenitis suppurativa.[34,101–104,107]

with HS report a diminished QoL (Figure 2).[34,101–106] When comparing DLQI scores of patients with HS with other dermatological patients or controls, patients with HS tend to have the highest scores.[103,105,107] Onderdijk *et al.* compared the DLQI scores of HS patients with patients with acne, eczema, psoriasis, skin tumors and other skin disease, and found that patients with HS had a significant higher scores than these other dermatological patients.[103] Basra *et al.* compared the DLQI scores of 45,710 patients with different skin diseases from 220 different studies (Figure 3).[108] HS had a mean score of 13.3, which was one of the highest scores; only burns (scars), erythropoietic protoporphyria, and hirsutism scored higher, suggesting that HS belongs in the top 5 skin diseases with the most negatively impacted QoL scores.[108]

To compare the effect of HS on QoL with other non-dermatological patients, the short form (SF)-36 can be used.[104,105] The SF-36 is a short survey to assess health-related QoL, in which a lower score indicates a greater impairment of QoL. When compared with diabetes mellitus with or without foot problems, breast cancer, IBD or stroke, HS patients still have the worst QoL scores (Table III).[104,105,109–112]

5.1.1 Causes of low quality of life in hidradenitis suppurativa

When examining predictors of low QoL, young age of onset of HS, a higher number of lesions per month, and a more severe disease are associated with a lower QoL.[101,105,106] On the DLQI, patients with Hurley stage III scored significantly higher than patients with Hurley stage I.[102,104] In addition, the Sartorius score also showed to have a significant correlation with the DLQI scores.[34] Questions on pain, discomfort and embarrassment scored the highest, indicating that these are important factors diminishing QoL.[34,101,103]

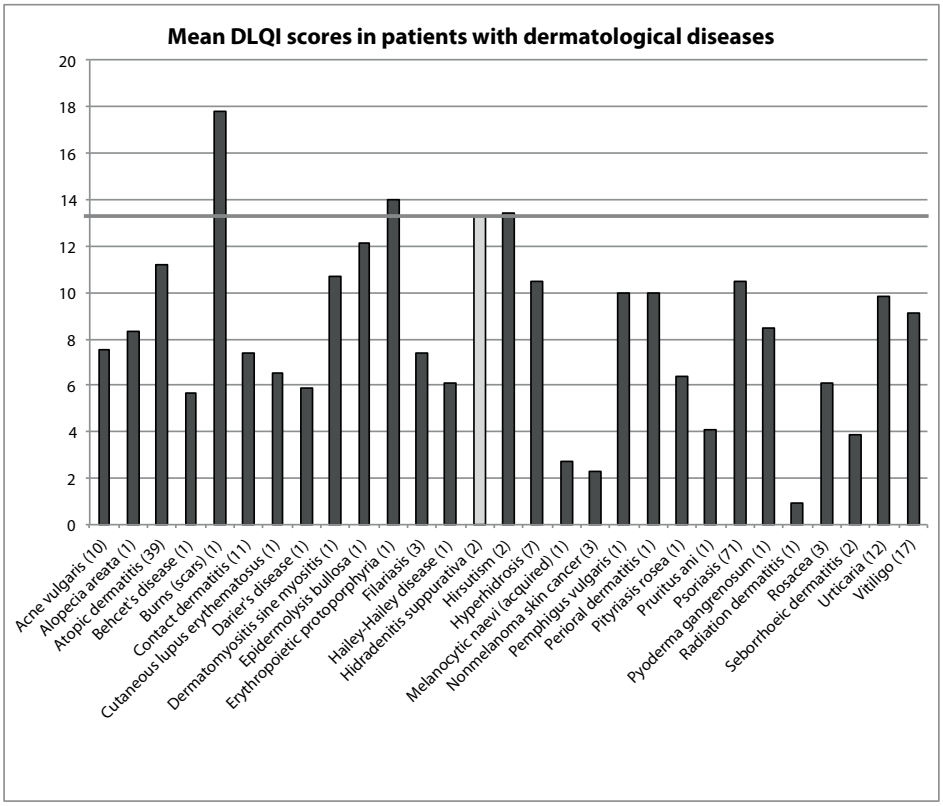


Figure 3. An overview of the Dermatological Life Quality Index (DLQI) scores in patients with multiple different dermatological diseases. In parentheses the number of studies is indicate on which the DLQI score is based.[108]

Fatigue also scores high,[106] which is consistent with the work by Matusiak *et al*;[102] they found that almost 40% of the HS patients had clinically significant fatigue, with a strong correlation between the Hurley stage and the level of fatigue.

5.2 Depression

HS is often associated with depression but the reported prevalence varies substantially across published studies. Shavit *et al.* investigated the prevalence of depression in a large database including 3,207 patients with HS, and found that almost 6% of the patients with HS suffered from depression.[113] Three studies using depression questionnaires found a prevalence of depression between 9% and 39%.[102,103,114] Unfortunately, all three used different depression questionnaires, making direct comparison impossible.[102,103,114] In two studies, disease severity correlated with the depression scores.[102,114] Onderdijk *et al.* could not confirm the association between depression and Hurley score, but they did find a correlation between depression and the number of lesions and flares in the last month.[103]

Table III. SF-36 scores of patients with hidradenitis suppurativa, diabetes mellitus, breast cancer, inflammatory bowel disease, stroke, and normative sample

SF-36 domain[a]	**HS**[105] n=60	**HS**[104] n=55	**DM**[109] n=49 Without foot problems	**DM**[109] n=47 with foot problems	**Breast cancer**[110] n=50	**IBD**[111] n=793	**Stroke**[112] n=111	**Normative sample**[105] n=3656
Physical functioning	71.3	47.0	79.0	42.0	85.3	78.4	67.5	84.5
Role physical	43.6	45.0	73.0	28.0	72.5	65.1	46.2	81.3
Bodily pain	44.5	440	78.0	59.0	72.1	64.7	64.2	73.5
General health	43.3	45.0	60.0	46.0	55.3	47.2	54.0	69.2
Vitality	40.4	47.0	66.0	54.0	73.6	54.5	51.4	60.1
Social functioning	52.5	43.0	83.0	66.0	67.2	75.0	64.5	81.6
Role emotional	42.9	46.0	82.0	71.0	71.3	72.4	50.7	82.2
Mental health	43.0	48.0	79.0	74.0	67.2	65.9	61.0	68.5
Mean	47.7	45.6	75.0	55.0	70.6	65.4	57.4	75.1

DM - diabetes mellitus; IBD - inflammatory bowel disease; HS - hidradenitis suppurativa

[a] Mean score per domain in which a lower score indicates a greater impairment of health related quality of life

5.3 Sexual distress

Patients often report that HS has a great influence on their sexual life. They feel embarrassed because of the inflammation and disfiguring scars, often located in intimate regions. They also suffer from pain that restrains them from having sexual intercourse. Patients report that their partners lose interest in sexual activity when they have active lesions.[115] To date, one study has investigated the influence of HS on sexual health. The investigators found a significant impairment of sexual health in patients with HS compared with age-, sex-, and BMI-matched controls.[116] Women with the same level of disease reported higher sexual distress than men, but surprisingly, there was no correlation between sexual functioning and disease severity. However, two patients without genital lesions had similar levels of sexual function as the healthy controls, suggesting that the location of inflammation was important in causing sexual distress.[116]

5.4 Work

Patients often report that because of the painful lesions they are unable to go to work and sometimes even lose their jobs because of the numerous sick days. Matusiak *et al.* found that patients were on average 33.6 days per year absent from work because of their HS.[117] Out of 30 patients, three reported losing their jobs in the two-year follow-up period because of frequent absences or inability to perform their work properly. Another seven patients reported they were not promoted because of their HS or had

disease-related obstacles regarding promotion or advancement;[117] however, other studies have found fewer missed work days.[103,118] Onderdijk *et al.* even found that patients with HS missed fewer work days than controls (3.1 days vs 7.1), although this difference was not significant.[103]

6. TREATMENTS

To date, there is no cure for HS; treatment generally consists of a combination of medication and surgery.[93] Unfortunately, large randomized controlled trials in HS are scarce and most studies are small and retrospective.[93] The medical treatment options of HS with their mode of action are extensively reviewed in chapter 9. In mild cases, topical application of clindamycin lotion or resorcinol can be sufficient,[119,120] whereas in more extensive cases systemic drug treatments are often needed.[93] When extensive sinus formation is present, surgical excision is necessary to achieve remission.[93] For every patient the most suitable treatment should be chosen based on the extensiveness of the disease and the preferences of the patient.

6.1 Antibiotics

The first step in the treatment of mild HS is often topical clindamycin 1% lotion. It is a simple, safe and effective treatment for patients with mild HS.[119] In more widespread disease, antibiotics from the tetracycline group (e.g. doxycycline or minocycline) can be effective when given for a longer period.[121] These antibiotics are mostly effective because of their anti-inflammatory properties. They are less effective in treating or preventing exacerbations of HS, since most bacteria cultured in HS are resistant for tetracyclines.[58] The next step in antibiotics is the combined therapy of clindamycin and rifampicin.[122–124] This combination has shown high remission rates, with up to 84% of the patients showing partial to complete response. However, patients mostly need this combination for a minimum of ten weeks to achieve remission.[122–124] In severe or therapy-resistant HS, the combination of rifampicin, moxifloxacin and metronidazole has shown good results, with 57% of the patients achieving complete remission.[125] However, most patients complain of side effects, mostly gastrointestinal problems, leading to early termination of the treatment. Unfortunately for all antibiotics, recurrence rates are high after discontinuation.[123,125]

6.2 Biologics

In moderate to severe HS that does not respond to antibiotic treatments, biologics are the next option. Especially TNF-α inhibitors (e.g. infliximab and adalimumab) have shown to be effective. However, even though biologics are often well tolerated and can

suppress the disease for a long period, they are seldom curative.[99,126,127] Adalimumab is the best documented biologic for the treatment of HS, and it is the only treatment proven effective in a large multicenter randomized placebo-controlled trial.[99] Every week 40 mg of adalimumab showed to be more effective than placebo; however, still only 18% of the patients reached the clinical endpoint (clear, moderate to mild response with a decrease of at least two grades) after sixteen weeks of treatment.[99] Long-term treatment is necessary to maintain disease suppression, because after discontinuation high recurrence rates have been reported.[128] Infliximab in a dosage of 5 mg/kg body weight, administered in week 0, 2, 6 and then every 8 weeks showed to be effective in patients with HS and is safe for long-term treatment of HS.[127,129] In a placebo-controlled trial, patients receiving infliximab showed a significant decrease in severity, with 47% having an excellent response. However, only 7% of the patients showed total clearance of the lesions.[127] In addition, relapse rates during treatment are high, half the patients showed relapse after a median treatment time of 37 weeks.[129] It has been suggested that a shorter treatment interval might be more effective in HS.[130] However, trials comparing different intervals regimes for HS are lacking.

6.3 Surgical treatment

Most patients with HS need at least one surgical procedure during their lifetime. This can be incision and drainage, excision of a single lesion, or wide surgical excisions.[93] Incision and drainage is performed to relief pain in patients with an acute inflammation;[131] mostly this is done at the emergency room. However, recurrence rates up to 100% have been reported, therefore incision and drainage is not an effective treatment in HS.[131] In mild cases, Hurley stage I or II, the lesions can also be excised and closed primarily using stiches. Recurrence rates of 34% have been reported after a follow-up of 27 months.[132] Therefore, for mild cases deroofing is more effective, with a recurrence rate of 17%.[133] During a deroofing the sinuses are explored using a blunt probe, whereafter the sinus roof is excised using electrosurgery. It is important that the wound edges are carefully examined for remaining sinus tracts. The wounds are mostly left open for healing by secondary intention.[133,134] In severe HS, when large areas are affected, extensive surgery is often needed.[135–137] During surgery, all affected tissue should be excised up to the healthy fat, and again all wound edges should be checked for remaining sinus tracks.[135,136] This can be done using electrosurgical wide or staged excision, for which the recurrence rates vary between 3% and 34%.[131,135–139] Different closure techniques have been described to close the large wounds. Rompel and Peters found no difference in recurrence rate between the different reconstruction techniques (primary closure, local flaps, multiple forms of skin plasty, free skin grafts and healing via secondary intention),[135] whereas Watson *et al*. showed that primary closure had a higher recurrence rate than closure via split-skin graft or local flap cover.[140] However, all studies use different

closure techniques and different definitions of recurrence, therefore direct comparison of these studies is impossible.

6.4 Lifestyle changes

Besides medical or surgical treatment, all patients with HS should be given lifestyle advice. As discussed in the above section, smoking and obesity are highly associated with HS. However, even though smoking is associated with the onset of HS and disease severity, it is not clear whether cessation of smoking can improve the disease course of HS. In a case report, two patients became disease-free after they stopped smoking.[141] However, the clinical impression is that cessation does not improve symptoms on short notice.[34,142] The long-term impact of smoking cessation is unknown. There is strong evidence that weight reductions aids towards disease remission. Kromann *et al.* investigated the impact of weight loss after bariatric surgery on HS symptoms. Half the patients who had symptoms before the surgery and who had lost more than 15% of their BMI, reported to be free of inflammations. Whereas another 20% of the patients reported fewer symptoms after the weight loss.[143] These results are supported by case reports of patients achieving disease remission after extensive weight loss.[68,144]

Patients often feel trapped in a negative cycle of lifestyle changes. When addressing these risk factors patients often respond that HS causes significant stress because of the painful inflammation, making it difficult to quit smoking. When they manage to quit smoking they frequently start eating more, resulting in weight gain, which results in more stress and feeling the need to restart smoking. Active involvement in sports to lose weight is often difficult because of the painful lesions. The net effect of these trade-offs can unfortunately substantially limit the ability to impact useful lifestyle changes. Nonetheless, patients should be encouraged to change their lifestyle, if possible with the help of "stop smoking" or "weight loss" programs.

7. AIMS OF THIS THESIS

HS is a chronic debilitating disease, and the diagnosis of HS comes with many uncertainties; the course of the disease is unknown, as is whether the disease will flare or if patients ever will be free of inflammation. In addition, there remains a great unmet need for better therapies and as of today, a cure is distant. Therefore, in this thesis we focused on the clinical aspects of HS.

The aim of the first part was to investigate factors associated with early onset, disease severity and remission. First, we wanted to determine the prevalence of early-onset HS, because our clinical impression contradicted with the literature that prepubertal onset of HS is rare. To do so, in **Chapter 2** we determined the prevalence of onset before the thirteenth birthday, and in addition determined risk factors for early-onset HS. Following in **Chapter 3**, we determined factors associated with disease severity, sex and family history. Last for **Chapter 4** we investigated the clinical course of HS, and determined the percentage of patients who became disease-free, 22 years after the diagnosis was set by a dermatologist. We also sought for factors that were associated with remission.

In the second part of this thesis we looked at two specific comorbidities of HS, namely anemia and inflammatory bowel disease (IBD). In **Chapter 5**, we reported on two patients with severe HS and concomitant anemia causing severe fatigue, and we reviewed the literature. While in **Chapter 6** the association between IBD and HS was further investigated. We determined the prevalence of IBD in patients with HS, and investigated whether patients with IBD and HS had a different HS phenotype.

The third part of this thesis is about the impact of HS on the lives of the patients. In small studies HS has shown to have great impact on sexual health. However, since large studies are lacking, we wanted to investigate the influence of HS on sexual health and quality of life in a large group of patients. The results of this questionnaire-based study are presented in **Chapter 7**. Besides a lower quality of life it is our clinical impression that patients with HS also have a lower social economic status (SES) than other dermatological patients. Therefore we compared the SES of HS patients with patients with other dermatological diseases in **Chapter 8**.

In the fourth part of this thesis we looked at the treatment options for HS. We start in **Chapter 9** with a comprehensive review of most medical treatments of HS with their mode of action. In **Chapter 10** we show the results of fumaric acids as a new treatment option for HS. Fumarates have proven to be very effective in patients with psoriasis due to their immunomodulating properties; therefore we hypothesized that they might also be effective in patients with HS. Finally, in **Chapter 11** we wanted to determine the outcome of wide surgical excision in patients with severe HS. To do so we retrospectively reviewed the recurrence rate and patients satisfaction of 260 surgical procedures performed in 86 patients with HS

REFERENCES

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

2 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

3 Velpeau ALA. Aisselle, phlegmons, abces. In: Adelon, Béclard, Berared et al, *Dictionnaire de médicine ou répertoire général des sciences médicales considérées sous le rapport théorique et pratique.* 2nd ed. Paris: Bechet Jeune.1832; 91–101.

4 Verneuil A. De L'hidrosadenite phlegmoneuse et des abces sudoripares. *Arch Gen Med* 1864; **2**: 537–557.

5 Lane JE. Hidrosadenitis axillaris of Verneuil. *Arch Derm Syphilol* 1933; **28**: 609–614.

6 Plewig G, Steger M. Acne inversa. Alias acne triad, acne tetrad or hidradenitis suppurativa. In: Marks R, Plewig G (eds). *Acne and related disorders*. London: Martin Dunitz. 1989; 345–357.

7 Plewig G, Kligman AM. Acne inversa. In: Plewig G, Kligman AM (eds). Acne and rosacea 2nd. Springer-Verlag Berlin Heidelber. 1993; 284–289.

8 Kamp S, Fiehn AM, Stenderup K, *et al.* Hidradenitis suppurativa: a disease of the absent sebaceous gland? Sebaceous gland number and volume are significantly reduced in uninvolved hair follicles from patients with hidradenitis suppurativa. *Br J Dermatol* 2011; **164**: 1017–1022.

9 Norris JFB, Cunliffe WJ. Failure of treatment of familial widespread hidradenitis suppurativa with isotretinoin. *Clin Exp Dermatol* 1986; **11**: 579–583.

10 Boer J, van Gemert MJP. Long-term results of isotretinoin in the treatment of 68 patients with hidradenitis suppurativa. *J Am Acad Dermatol* 1999; **40**: 73–76.

11 Wittmann DH, Schein M, Seoane D, *et al.* Pyoderma fistulans sinifica (fox den disease): a distinctive soft-tissue infection. *Clin Infect Dis* 1995; **21**: 162–170.

12 Stehr RC, Kim N, LoGiudice JA, Ludwig K. Fox Den Disease: an interesting case following delayed diagnosis. *Wounds* 2015; **27**: 170–173.

13 van Everdingen JJE, Sillevis Smitt JH. Acne vulgaris. In: van Everdingen JJE, Sillevis Smitt JH (eds) *Dermato-venereologie voor eerste lijn* 2e druk. Amsterdam. 1983; 119.

14 Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. *J Am Acad Dermatol* 2009; **60**: 539–561.

15 Canoui-Poitrine F, Le Thuaut A, Revuz JE, *et al.* Identification of three hidradenitis suppurativa phenotypes: Latent class analysis of a cross-sectional study. *J Invest Dermatol* 2013; **133**: 1506–1511.

16 van der Zee HH, Jemec GBE. New insights into the diagnosis of hidradenitis suppurativa: Clinical presentations and phenotypes. *J Am Acad Dermatol* 2015; **73**: S23–S26.

17 Jemec GBE, Heidenheim M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential precursor lesions. *J Am Acad Dermatol* 1996; **35**: 191–194.

18 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

19 Cosmatos I, Matcho A, Weinstein R, *et al.* Analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States. *J Am Acad Dermatol* 2013; **68**: 412–419.

20 Shahi V, Alikhan A, Vazquez BG, *et al.* Prevalence of hidradenitis suppurativa: a population-based study in Olmsted County, Minnesota. *Dermatology* 2014; **229**: 154–158.

21 Saunte DM, Boer J, Stratigos A, *et al.* Diagnostic delay in hidradenitis suppurativa is a global problem. *Br J Dermatol* 2015; **Epub ahead of print**.

22 Von der Werth JM, Williams HC. The natural history of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2000; **14**: 389–392.

23 Canoui-Poitrine F, Revuz JE, Wolkenstein P, *et al.* Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. *J Am Acad Dermatol* 2009; **61**: 51–57.

24 Mengesha YM, Holcombe TC, Hansen RC. Prepubertal hidradenitis suppurativa: two case reports and review of the literature. *Pediatr Dermatol* 1999; **16**: 292–296.

25 Bettoli V, Ricci M, Zauli S, Virgili A. Hidradenitis suppurativa–acne inversa: a relevant dermatosis in pediatric age. *Br J Dermatol* 2015; **Epub ahead of print**.

26 Von der Werth JM, Williams HC, Raeburn JA. The clinical genetics of hidradenitis suppurativa revisited. *Br J Dermatol* 2000; **142**: 947–953.

27 van der Zee HH, Laman JD, Boer J, Prens EP. Hidradenitis suppurativa: viewpoint on clinical phenotyping, pathogenesis and novel treatments. *Exp Dermatol* 2012; **21**: 735–739.

28 Yu C-W, Cook MG. Hidradenitis suppurativa: a disease of follicular epithelium, rather than apocrine glands. *Br J Dermatol* 1990; **122**: 763–769.

29 Boer J, Weltevreden EF. Hidradenitis suppurativa or acne inversa. A clinicopathological study of early lesions. *Br J Dermatol* 1996; **135**: 721–725.

30 Jemec GBE, Hansen U. Histology of hidradenitis suppurativa. *J Am Acad Dermatol* 1996; **34**: 994–999.

31 von Laffert M, Helmbold P, Wohlrab J, *et al.* Hidradenitis suppurativa (acne inversa): early inflammatory events at terminal follicles and at interfollicular epidermis. *Exp Dermatol* 2010; **19**: 533–537.

32 Von Laffert M, Stadie V, Wohlrab J, Marsch WC. Hidradenitis suppurativa/acne inversa: bilocated epithelial hyperplasia with very different sequelae. *Br J Dermatol* 2011; **164**: 367–371.

33 Vazquez BG, Alikhan A, Weaver AL, *et al.* Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol* 2013; **133**: 97–103.

34 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

35 König A, Lehmann C, Rompel R, Happle R. Cigarette smoking as a triggering factor of hidradenitis suppurativa. *Dermatology* 1999; **198**: 261–264.

36 Happle R, König A. Smoker's boils. *Dermatology* 2011; **222**: 282–284.

37 Kurzen H, Kurokawa I, Jemec GBE, *et al.* What causes hidradenitis suppurativa? *Exp Dermatol* 2008; **17**: 455–456.

38 Sørensen LT, Nielsen HB, Kharazmi A, Gottrup F. Effect of smoking and abstention on oxidative burst and reactivity of neutrophils and monocytes. *Surgery* 2004; **136**: 1047–1053.

39 Aoshiba K, Nagai A, Yasui S, Konno K. Nicotine prolongs neutrophil survival by suppressing apoptosis. *J Lab Clin Med* 1996; **127**: 186–194.

40 Blandina P, Fantozzi R, Mannaioni PF, Masini E. Characteristics of histamine release evoked by acetylcholine in isolated rat mast cells. *J Physiol* 1980; **301**: 281–293.

41 Hana A, Booken D, Henrich C, *et al.* Functional significance of non-neuronal acetylcholine in skin epithelia. *Life Sci* 2007; **80**: 2214–2220.

42 Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. *J Am Acad Dermatol* 2007; **56**: 901–916.

43 Coppack SW. Pro-inflammatory cytokines and adipose tissue. *Proc Nutr Soc* 2001; **60**: 349–356.

44 van der Zee HH, de Ruiter L, van den Broecke DG, *et al.* Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. *Br J Dermatol* 2011; **164**: 1292–1298.

45 Fitzsimmons JS, Guilbert PR. A family study of hidradenitis suppurativa. *J Med Genet* 1985; **22**: 367–373.

46 Fitzsimmons JS, Guilbert PR, Fitzsimmons EM. Evidence of genetic factors in hidradenitis suppurativa. *Br J Dermatol* 1985; **113**: 1–8.

47 Pink AE, Simpson MA, Brice GW, *et al.* PSENEN and NCSTN mutations in familial hidradenitis suppurativa (Acne Inversa). *J Invest Dermatol* 2011; **131**: 1568–1570.

48 Pink AE, Simpson MA, Desai N, *et al.* γ-Secretase mutations in hidradenitis suppurativa: new insights into disease pathogenesis. *J Invest Dermatol* 2012; **133**: 601–607.

49 Wang B, Yang W, Wen W, *et al.* γ-secretase gene mutations in familial acne inversa. *Science* 2010; **330**: 1065.

50 Melnik BC, Plewig G. Impaired Notch-MKP-1 signalling in hidradenitis suppurativa: an approach to pathogenesis by evidence from translational biology. *Exp Dermatol* 2013; **22**: 172–177.

51 Van der Zee HH, Van Der Woude CJ, Florencia EF, Prens EP. Hidradenitis suppurativa and inflammatory bowel disease: are they associated? Results of a pilot study. *Br J Dermatol* 2010; **162**: 195–197.

52 Nazary M, van der Zee HH, Prens EP, *et al.* Pathogenesis and pharmacotherapy of Hidradenitis suppurativa. *Eur J Pharmacol* 2011; **672**: 1–8.

53 Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011; **65**: 790–798.

54 Kelly G, Hughes R, Mc Garry T, *et al.* Dysregulated cytokine expression in lesional and non-lesional skin in Hidradenitis suppurativa. *Br J Dermatol* 2015; **173**: 1431–1439.

55 Van der Zee HH, Laman JD, de Ruiter L, *et al.* Adalimumab (antitumour necrosis factor-α) treatment of hidradenitis suppurativa ameliorates skin inflammation: an in situ and ex vivo study. *Br J Dermatol* 2012; **166**: 298–305.

56 Lapins J, Jarstrand C, Emtestam L. Coagulase-negative staphylococci are the most common bacteria found in cultures from the deep portions of hidradentis suppurativa lesions, as obtained by carbon dioxide laser surgery. *Br J Dermatol* 1999; **140**: 90–95.

57 Sartorius K, Killasli H, Oprica C, *et al.* Bacteriology of hidradenitis suppurativa exacerbations and deep tissue cultures obtained during carbon dioxide laser treatment. *Br J Dermatol* 2012; **166**: 879–883.

58 Matusiak Ł, Bieniek A, Szepietowski JC. Bacteriology of hidradenitis suppurativa - which antibiotics are the treatment of choice? *Acta Derm Venereol* 2014; **94**: 699–702.

59 Jemec GBE, Faber M, Gutschik E, Wendelboe P. The bacteriology of hidradenitis suppurativa. *Dermatology* 1996; **193**: 203–206.

60 Nikolakis G, Join-Lambert O, Karagiannidis I, *et al.* Bacteriology of hidradenitis suppurativa/acne inversa: A review. *J Am Acad Dermatol* 2015; **73**: S12–S18.

61 Ring HC, Riis Mikkelsen P, Miller IM, *et al.* The bacteriology of hidradenitis suppurativa: a systematic review. *Exp Dermatol* 2015; **24**: 727–731.

62 Guet-Revillet H, Coignard-Biehler H, Jais J-P, *et al.* Bacterial Pathogens Associated with Hidradenitis Suppurativa, France. *Emerg Infect Dis* 2014; **20**: 1990–1998.

63 Mortimer PS, Dawber RP, Gales MA, Moore RA. Mediation of hidradenitis suppurativa by androgens. *Br Med J (Clin Res Ed)* 1986; **292**: 245.

64 Jemec GBE. The symptomatology of hidradenitis suppurativa in women. *Br J Dermatol* 1988; **119**: 345–350.

65 Barth JH, Layton AM, Cunliffe WJ. Endocrine factors in pre-and postmenopausal women with hidradenitis suppurativa. *Br J Dermatol* 1996; **134**: 1057–1059.

66 Harrison BJ, Read GF, Hughes LE. Endocrine basis for the clinical presentation of hidradenitis suppurativa. *Br J Surg* 1988; **75**: 972–975.

67 Morgan WP, Leicester G. The role of depilation and deodorants in hidradenitis suppurativa. *Arch Dermatol* 1982; **118**: 101–102.

68 Boer J. Resolution of hidradenitis suppurativa after weight loss by dietary measures, especially on frictional locations. *J Eur Acad Dermatol Venereol* 2015; **Epub ahead of print**.

69 Dufour DN, Bryld LE, Jemec GBE. Hidradenitis suppurativa complicating naevus comedonicus: the possible influence of mechanical stress on the development of hidradenitis suppurativa. *Dermatology* 2010; **220**: 323–325.

70 de Winter K, van der Zee HH, Prens EP. Is mechanical stress an important pathogenic factor in hidradenitis suppurativa? *Exp Dermatol* 2012; **21**: 176–177.

71 Chicarilli ZN. Follicular occlusion triad: hidradenitis suppurativa, acne conglobata, and dissecting cellulitis of the scalp. *Ann Plast Surg* 1987; **18**: 230–237.

72 Scheinfeld NS. A case of dissecting cellulitis and a review of the literature. *Dermatol Online J* 2003; **9**: 8.

73 Fimmel S, Zouboulis CC. Comorbidities of hidradenitis suppurativa (acne inversa). *Dermatoendocrinol* 2010; **2**: 9–16.

74 Church JM, Fazio VW, Lavery IC, *et al.* The differential diagnosis and comorbidity of hidradenitis suppurativa and perianal Crohn's disease. *Int J Colorectal Dis* 1993; **8**: 117–119.

75 van der Zee HH, de Winter K, Van Der Woude CJ, Prens EP. The prevalence of hidradenitis suppurativa in 1093 patients with inflammatory bowel disease. *Br J Dermatol* 2014; **171**: 673–675.

76 Kamal N, Cohen BL, Buche S, *et al.* Features of patients with Crohn's disease and hidradenitis suppurativa. *Clin Gastroenterol Hepatol* 2016; **14**: 71–79.

77 Yadav S, Singh S, Varayil JE, *et al.* Hidradenitis suppurativa in patients with inflammatory bowel disease: a population-based cohort study in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2016; **14**: 65–70.

78 Janse IC, Koldijk MJ, Spekhorst LM, *et al.* Identification of clinical and genetic parameters associated with hidradenitis suppurativa in inflammatory bowel disease. *Inflamm Bowel Dis* 2016; **22**: 106–113.

79 Roussomoustakaki M, Dimoulios P, Chatzicostas C, *et al.* Hidradenitis suppurativa associated with Crohn's disease and spondyloarthropathy: response to anti-TNF therapy. *J Gastroenterol* 2003; **38**: 1000–1014.

80 Blazquez I, Gonzalez-Lama Y, Roustan G. Crohn's disease and Hidradenitis suppurativa. An uncommon association that responds to Infliximab. *J Crohn's Colitis* 2013; **7**: e717–e718.

81 Attanoos RL, Appleton MAC, Hughes LE, *et al.* Granulomatous hidradenitis suppurativa and cutaneous Crohn's disease. *Histopathology* 1993; **23**: 111–115.

82 Roy MK, Appleton MAC, Delicata RJ, *et al.* Probable association between hidradenitis suppurativa and Crohn's disease: significance of epithelioid granuloma. *Br J Surg* 1997; **84**: 375–376.

83 Miller IM, Ellervik C, Vinding GR, *et al.* Association of metabolic syndrome and hidradenitis suppurativa. *JAMA dermatology* 2014; **150**: 1273–1280.

84 Shlyankevich J, Chen AJ, Kim GE, Kimball AB. Hidradenitis suppurativa is a systemic disease with substantial comorbidity burden: A chart-verified case-control analysis. *J Am Acad Dermatol* 2014; **71**: 1144–1150.

85 Shalom G, Freud T, Harman-Boehm I, *et al.* Hidradenitis suppurativa and metabolic syndrome: a comparative cross-sectional study of 3207 patients. *Br J Dermatol* 2015; **173**: 464–470.

86 Tzellos T, Zouboulis CC, Gulliver W, *et al.* Cardiovascular disease risk factors in patients with hidradenitis suppurativa: a systematic review and meta-analysis of observational studies. *Br J Dermatol* 2015; **Epub ehead of print**.

87 Hsiao JL, Antaya RJ, Berger T, *et al.* Hidradenitis suppurativa and concomitant pyoderma gangrenosum: a case series and literature review. *Arch Dermatol* 2010; **146**: 1265–1270.

88 Ruocco E, Sangiuliano S, Gravina AG, *et al.* Pyoderma gangrenosum: an updated review. *J Eur Acad Dermatol Venereol* 2009; **23**: 1008–1017.

89 Bhalla R, Sequeira W. Arthritis associated with hidradenitis suppurativa. *Ann Rheum Dis* 1994; **53**: 64–66.

90 Leybishkis B, Fasseas P, Ryan KF, Roy R. Hidradenitis suppurativa and acne conglobata associated with spondyloarthropathy. *Am J Med Sci* 2001; **321**: 195–197.

91 Thein M, Hogarth MB, Acland K. Seronegative arthritis associated with the follicular occlusion triad. *Clin Exp Dermatol* 2004; **29**: 550–552.

92 Richette P, Molto A, Viguier M, *et al.* Hidradenitis suppurativa associated with spondyloarthritis—results from a multicenter national prospective study. *J Rheumatol* 2014; **41**: 490–494.

93 Zouboulis CC, Desai N, Emtestam L, *et al.* European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; **29**: 619–644.

94 Hidradenitis Suppurativa Foundation. Available from: www.hs-foundation.org

95 Wollina U, Koch A, Heinig B, *et al.* Acne inversa (Hidradenitis suppurativa): A review with a focus on pathogenesis and treatment. *Indian Dermatol Online J* 2013; **4**: 2–11.

96 Esmann S, Dufour DN, Jemec GBE. Questionnaire-based diagnosis of hidradenitis suppurativa: specificity, sensitivity and positive predictive value of specific diagnostic questions. *Br J Dermatol* 2010; **163**: 102–106.

97 Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. In Roenigh RRH (eds). *Dermatologic Surgery.* Marcel Dekker, New York.1989; 729–739.

98 Sartorius K, Lapins J, Emtestam L, Jemec GBE. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. *Br J Dermatol* 2003; **149**: 211–213.

99 Kimball AB, Kerdel F, Adams D, *et al.* Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med* 2012; **157**: 846–855.

100 Kimball AB, Jemec GBE, Yang M, *et al.* Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol* 2014; **171**: 1434–1442.

101 Von der Werth JM, Jemec GBE. Morbidity in patients with hidradenitis suppurativa. *Br J Dermatol* 2001; **144**: 809–813.

102 Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol* 2010; **90**: 264–268.

103 Onderdijk AJ, van der Zee HH, Esmann S, *et al.* Depression in patients with hidradenitis suppurativa. *J Eur Acad Dermatology Venereol* 2013; **27**: 473–478.

104 Alavi A, Anooshirvani N, Kim WB, *et al.* Quality-of-life impairment in patients with hidradenitis suppurativa: A canadian study. *Am J Clin Dermatol* 2015; **16**: 61–65.

105 Wolkenstein P, Loundou A, Barrau K, *et al.* Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. *J Am Acad Dermatol* 2007; **56**: 621–623.

106 Benjamins M, van der Wal VB, de Korte J. Kwaliteit van leven bij Nederlandse patiënten met hidradenitis suppurativa (acne inversa)[English abstract]. *Ned Tijdschr Derm Venereol* 2009; **19**: 446–450.

107 Vinding GR, Knudsen KM, Ellervik C, *et al.* Self-reported skin morbidities and health-related quality of life: a population-based nested case-control study. *Dermatology* 2014; **228**: 261–268.

108 Basra MKA, Fenech R, Gatt RM, *et al.* The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**: 997–1035.

109 Hoban C, Sareen J, Henriksen CA, *et al.* Mental health issues associated with foot complications of diabetes mellitus. *Foot Ankle Surg* 2015; **21**: 49–55.

110 Shor V, Grinstein-Cohen O, Reinshtein J, *et al.* Health-related quality of life and sense of coherence among partners of women with breast cancer in Israel. *Eur J Oncol Nurs* 2015; **19**: 18–22.

111 Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, *et al.* Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. *Inflamm Bowel Dis* 2014; **20**: 92–102.

112 Cerniauskaite M, Quintas R, Koutsogeorgou E, *et al.* Quality-of-life and disability in patients with stroke. *Am J Phys Med Rehabil* 2012; **91**: S39–S47.

113 Shavit E, Dreiher J, Freud T, *et al.* Psychiatric comorbidities in 3207 patients with hidradenitis suppurativa. *J Eur Acad Dermat Venereol* 2015; **29**: 371–376.

114 Kurek A, Peters J, Milena E, *et al.* Depression is a frequent co-morbidity in patients with acne inversa. *J Dtsch Dermatol Ges* 2013; **11**: 743–749.

115 Esmann S, Jemec GB. Psychosocial impact of hidradenitis suppurativa: a qualitative study. *Acta Derm Venereol* 2011; **91**: 328–332.

116 Kurek A, Peters EMJ, Chanwangpong A, *et al.* Profound disturbances of sexual health in patients with acne inversa. *J Am Acad Dermatol* 2012; **67**: 422–428.

117 Matusiak Ł, Bieniek A, Szepietowski JC. Hidradenitis suppurativa markedly decreases quality of life and professional activity. *J Am Acad Dermatol* 2010; **62**: 706–708.

118 Jemec GBE, Heidenheim M, Nielsen NH. Hidradenitis suppurativa-characteristics and consequences. *Clin Exp Dermatol* 1996; **21**: 419–423.

119 Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. *Int J Dermatol* 1983; **22**: 325–328.

120 Boer J, Jemec GBE. Resorcinol peels as a possible self-treatment of painful nodules in hidradenitis suppurativa. *Clin Exp Dermatol* 2010; **35**: 36–40.

121 Collier F, Smith RC, Morton CA. Diagnosis and management of hidradenitis suppurativa. *BMJ* 2013; **346**: f2121.

122 Gener G, Canoui-Poitrine F, Revuz JE, *et al.* Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. *Dermatology* 2009; **219**: 148–154.

123 van der Zee HH, Boer J, Prens EP, Jemec GBE. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. *Dermatology* 2009; **219**: 143–147.

124 Bettoli V, Zauli S, Borghi A, *et al.* Oral clindamycin and rifampicin in the treatment of hidradenitis suppurativa-acne inversa: a prospective study on 23 patients. *J Eur Acad Dermatol Venereol* 2014; **28**: 125–126.

125 Join-Lambert O, Coignard H, Jais J, *et al.* Efficacy of rifampin-moxifloxacin-metronidazole combination therapy in hidradenitis suppurativa. *Dermatology* 2011; **222**: 49–58.

126 Blok JL, van Hattem S, Jonkman MF, Horváth B. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. *Br J Dermatol* 2013; **168**: 243–252.

127 Grant A, Gonzalez T, Montgomery MO, *et al.* Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol* 2010; **62**: 205–217.

128 Miller I, Lynggaard CD, Lophaven S, *et al.* A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. *Br J Dermatol* 2011; **165**: 391–398.

129 Paradela S, Rodríguez-Lojo R, Fernández-Torres R, *et al.* Long-term efficacy of infliximab in hidradenitis suppurativa. *J Dermatolog Treat* 2012; **23**: 278–283.

130 Moriarty B, Jiyad Z, Creamer D. Four-weekly infliximab in the treatment of severe hidradenitis suppurativa. *Br J Dermatol* 2014; **170**: 986–987.

131 Ritz JP, Runkel N, Haier J, Buhr HJ. Extent of surgery and recurrence rate of hidradenitis suppurativa. *Int J Colorectal Dis* 1998; **13**: 164–168.

132 Van Rappard DC, Mooij JE, Mekkes JR. Mild to moderate hidradenitis suppurativa treated with local excision and primary closure. *J Eur Acad Dermatol Venereol* 2012; **26**: 898–902.

133 van der Zee HH, Prens EP, Boer J. Deroofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. *J Am Acad Dermatol* 2010; **63**: 475–480.

134 Hattem S, Spoo JR, Horváth B, *et al.* Surgical treatment of sinuses by deroofing in hidradenitis suppurativa. *Dermatol Surg* 2012; **38**: 494–497.

135 Rompel R, Petres J. Long-term results of wide surgical excision in 106 patients with hidradenitis suppurativa. *Dermatol Surg* 2000; **26**: 638–643.

136 Blok JL, Boersma M, Terra JB, *et al.* Surgery under general anaesthesia in severe hidradenitis suppurativa: a study of 363 primary operations in 113 patients. *J Eur Acad Dermatol Venereol* 2015; **29**: 1590–1597.

137 Bieniek A, Matusiak L, Okulewicz-Gojlik D, Szepietowski JC. Surgical treatment of hidradenitis suppurativa: experiences and recommendations. *Dermatol Surg* 2010; **36**: 1998–2004.

138 Bohn J, Svensson H. Surgical treatment of hidradenitis suppurativa. *Scand J Plast Reconstr Surg Hand Surg* 2001; **35**: 305–309.

139 Alharbi Z, Kauczok J, Pallua N. A review of wide surgical excision of hidradenitis suppurativa. *BMC Dermatol* 2012; **12**: 9.

140 Watson JD. Hidradenitis suppurativa—a clinical review. *Br J Plast Surg* 1985; **38**: 567–569.

141 Simonart T. Hidradenitis suppurativa and smoking. *J Am Acad Dermatol* 2010; **62**: 149–150.

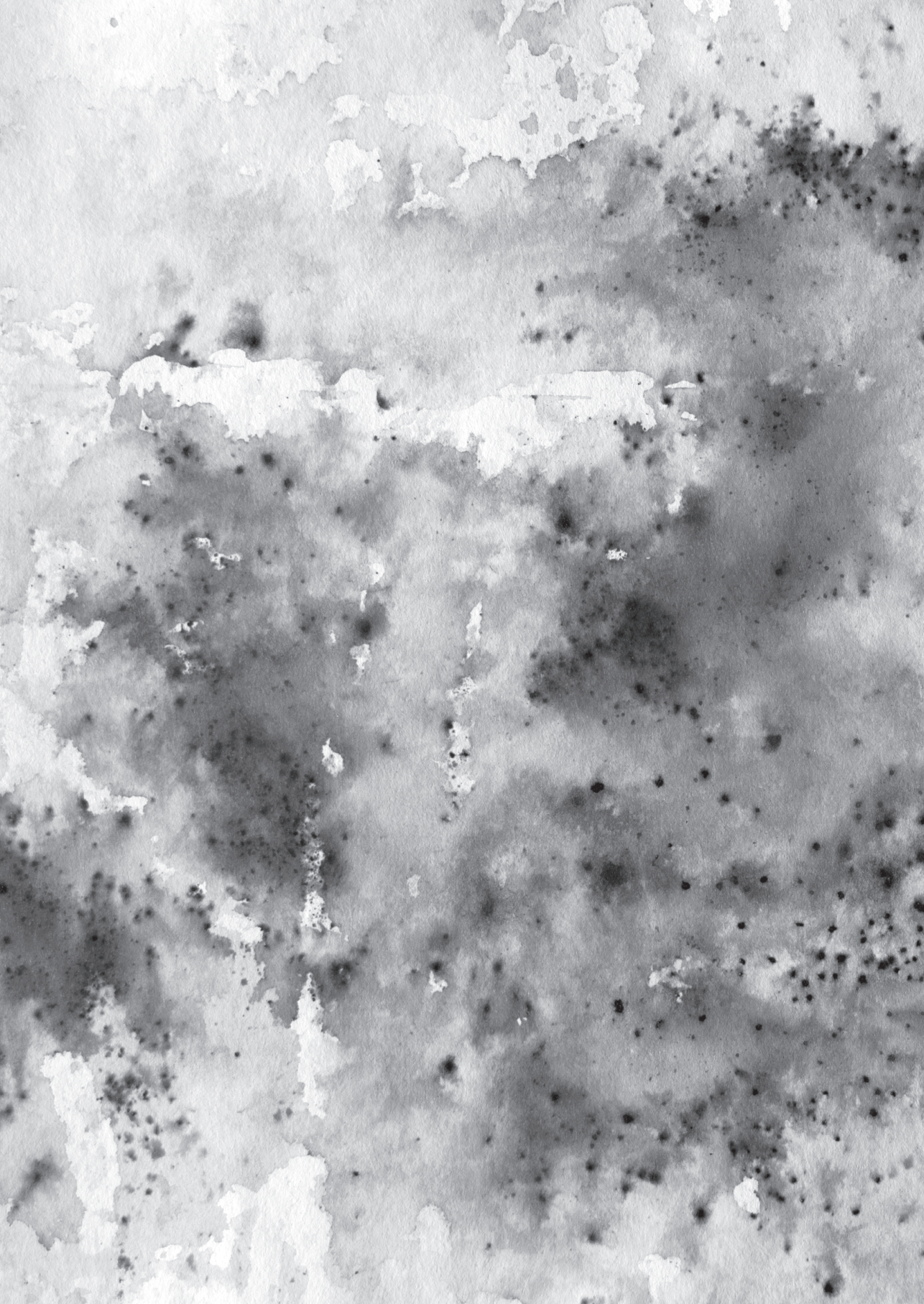
142 Matusiak Ł, Bieniek A, Szepietowski JC. Hidradenitis suppurativa and associated factors: still unsolved problems. *J Am Acad Dermatol* 2009; **61**: 362–365.

143 Kromann C, Ibler KS, Kristiansen V, Jemec GB. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol* 2014; **94**: 553–557.

144 Thomas CL, Gordon KD, Mortimer PS. Rapid resolution of hidradenitis suppurativa after bariatric surgical intervention. *Clin Exp Dermatol* 2014; **39**: 315–318.

Part I

Onset and Clinical Course of Hidradenitis Suppurativa



Chapter 2

Correlation of early-onset hidradenitis suppurativa with stronger genetic susceptibility and more widespread involvement

Inge E. Deckers, Hessel H. van der Zee,
Jurr Boer, Errol P. Prens

J Am Acad Dermatol. 2015;72:485-488

ABSTRACT

Background: The reported mean age of onset of hidradenitis suppurativa (HS) is between 20 and 24 years. Prepubertal onset is thought to be rare.

Objective: We sought to determine the prevalence of early-onset HS and to compare clinical characteristics between early-onset and normal-onset HS in a retrospective study.

Methods: Data were collected from 855 HS patients. Early-onset HS was defined as onset before the thirteenth birthday. Clinical characteristics were analyzed in relation to the age of onset.

Results: In all, 66 patients (7.7%) reported early-onset HS. A family history of HS was significantly more prevalent in early-onset patients (55.6% vs 34.2%; OR 2.1, 95% CI 1.2-3.6; $P = 0.006$). They developed inflammatory lesions at more body sites than patients with normal-onset HS (OR 3.0, 95% CI 1.8-4.9; $P < 0.001$). Distribution of the Hurley stages of severity showed no differences between the two groups (OR 1.1, 95% CI 0.7-1.8; $P = 0.72$).

Limitations: Some data were based on patient-reported information.

Conclusion: Early-onset HS occurs more frequently than previously believed. Patients with early-onset HS often report a family history of HS and develop lesions at more body sites.

INTRODUCTION

Hidradenitis suppurativa (HS), is characterized by recurrent inflammatory nodules at intertriginous body sites.[1,2] Onset of HS is generally after puberty, typically between the age of 20 and 24 years.[3–5] Prepubertal onset is estimated to occur in 2% of patients with HS.[6,7] When several of our patients reported onset of HS in their early teens, we sought to determine the prevalence of early-onset HS and to analyze the clinical characteristics of patients with HS in relation to the age of onset.

METHODS

Patients

We collected data from 855 patients given the diagnosis of HS between 2007 and 2014 in The Netherlands at the Department of Dermatology at the Erasmus University Medical Center, Rotterdam; the Deventer Hospital, Deventer; and the Department of Plastic Surgery at the Diaconessenhuis, Leiden. Data extraction took place partly from our HS database, also used by Schrader *et al*.[5] For this type of retrospective analysis, no medical ethical committee approval is required under Dutch law.

Data collection

Patient characteristics were collected from the medical files. A family history was considered positive when a first- or second-degree relative had HS. The Hurley classification was used to assess disease severity.[2] Body sites counted were: axillary, inguinal/genital, perianal, gluteal, abdominal and (infra) mammary. Normal weight was defined as a body mass index (BMI) below 25 kg/m^2, overweight as a BMI between 25 and 30 kg/m^2, and patients with a BMI above 30 kg/m^2 were categorized as obese.

Early- and normal-onset HS

Early-onset HS was defined as reported onset of disease before the thirteenth birthday. This cutoff point was chosen based on the mean age at menarche of 13.5 years in The Netherlands.[8] In general, puberty occurs later in boys. Therefore, it is conceivable that most patients with onset before their thirteenth birthday were prepubertal or in early puberty.

Data analysis

Statistical analysis was performed using SPSS 21 (IBM Corp, Armonk, NY). Independent *t*-tests were performed for nominal data, presented as mean ± standard deviation (SD). Pearson chi-square test was used for categorical data, and presented as number

(%). Binary logistic regression was used to investigate the effect of family history on early-onset HS, corrected for age and gender. As a second step we took early-onset as a predictor for disease severity, i.e. Hurley stage and number of locations affected. Here the response variables were ordinal and we used ordinal logistic regression, correcting for age and gender, presented as odds ratio (OR) with the 95% confidence interval (CI). *P*-values less than 0.05 were considered significantly different.

RESULTS

A total of 620 females and 235 males, mean age 37.9 ± 12.8 years, were included (Table I). Body sites most frequently affected were the inguinal/genital (89.7%), axillary (64.3%) and gluteal (41.2%) areas. The (infra) mammary (20.7%), perianal (19.5%) and abdominal (16.7%) regions were least affected. Most patients were current smokers (70.5%) or ex-smokers (14.2%), who started smoking at a mean age of 16.1 ± 3.9 years.

Early-onset HS associated with a positive family history of HS and more widespread disease

Early onset was reported by 66 patients (7.7%) and was related to a significantly higher percentage reporting a family history of HS (55.6% vs 34.2%; $P = 0.001$); this remained significant after correcting for age and gender (OR 2.1, 95% CI 1.2-3.6; $P = 0.006$). Early onset was associated with significantly more affected body sites (Table I). This association remained significant after correcting for age and gender (OR 3.0, 95% CI 1.8-4.9; $P < 0.001$). No difference was found in the distribution of Hurley stages, even after correcting for age and gender (OR 1.1, 95% CI 0.7-1.8; $P = 0.72$).

Fewer early-onset patients were smokers whereas there was no difference in the BMI

Of the 696 current smokers and ex-smokers, only a few of the early-onset group reported smoking before the onset of HS, whereas most of the normal-onset group had smoked before they developed symptoms (3/46, 6.5% vs 568/650, 87.4%; $P < 0.001$). There was no difference in weight in the BMI sub-groups (Table I), nor in mean BMI (28.6 ± 7.0 vs 28.0 ± 6.0; $P = 0.48$) between early-onset and normal-onset HS.

No differences in comorbidities between early-onset and normal-onset HS

No difference was found among the percentage of patients reporting acne during puberty (15/56, 26.8% vs 146/580, 25.6%; $P = 0.12$), concomitant arthritis (3/61, 4.9% vs 38/645, 5.9%; $P = 0.09$) or inflammatory bowel disease (1/66, 1.5% vs 24/784, 3.1%; $P = 0.63$).

Table I. General characteristics and comparison of patients with early-onset versus normal-onset hidradenitis suppurativa

	All patients (n=855)	**Early-onset HS**[a] (n=66)	**Normal-onset HS**[b] (n=789)	***P*-value**[c]
Gender, n (%)				
- Male	235 (27.5)	8 (12.1)	227 (28.8)	**0.004**
- Female	620 (72.5)	58 (87.9)	562 (71.2)	
Age years, mean ± SD	37.9 ± 12.8	31.5 ± 13.2	38.5 ± 12.6	**<0.001**
Disease duration years, mean ± SD	13.8 ± 11.1	20.7 ± 13.4	13.3 ± 10.6	**<0.001**
Family history, n (%)				
- Positive	290 (35.8)	35 (55.6)	255 (34.2)	**0.001**
- Negative	519 (64.2)	28 (44.4)	491 (65.8)	
- Unknown	46	3	43	
Hurley stage, n (%)				
- Stage I	392 (45.8)	33 (50.0)	359 (45.5)	0.37
- Stage II	351 (41.1)	28 (42.4)	323 (40.9)	
- Stage III	112 (13.1)	5 (7.6)	107 (13.6)	
No. of body sites affected, n (%)				
- 1-2 sites	470 (55.2)	23 (34.9)	447 (56.9)	**<0.001**
- 3-4 sites	312 (36.6)	29 (43.9)	283 (36.0)	
- 5-6 sites	70 (8.2)	14 (21.2)	56 (7.1)	
- Unknown	3	-	3	
Smoking status, n (%)				
- Current smoker	600 (70.5)	37 (56.1)	563 (71.7)	**0.01**
- Ex-smoker	121 (14.2)	11 (16.7)	110 (14.0)	
- Nonsmoker	130 (15.3)	18 (27.3)	112 (14.3)	
- Unknown	4	-	4	
BMI kg/m^2, n (%)[d]				
- Normal weight	296 (36.0)	23 (37.1)	273 (35.9)	0.97
- Overweight	264 (32.1)	19 (30.6)	245 (32.2)	
- Obese	263 (31.9)	20 (32.3)	243 (31.9)	
- Unknown	32	4	28	

BMI - body mass index; HS - hidradenitis suppurativa

[a] Age of onset before 13th birthday

[b] Age of onset after 13th birthday

[c] Independent *t*-test for continuous data and two-sided chi-square test for categorical data

[d] Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

DISCUSSION

In this retrospective study of 855 patients, 66 (7.7%) reported early-onset HS. This is higher than previously reported (2%),[7] indicating that early-onset HS is not so rare. Our results suggest that for HS, as with psoriasis and atopic dermatitis,[9,10] clinically different disease subsets can be distinguished based on age of onset.

In the early-onset group 56% reported a family history of HS, a higher proportion than the generally reported 35%.[3,11] This supports the findings of previous studies that patients with a family history of HS develop HS at an earlier age.[5,11] It is conceivable that a genetic predisposition influences the age of onset. Von der Werth and Williams suggested that age of onset also influences the prognosis of HS.[12] Our data confirm that early onset is associated with the development of a more widespread disease. Although a greater number of affected body sites would suggest more severe disease, this was not reflected in Hurley staging. A major shortcoming of the Hurley score is that it does not take the number of affected body areas into account. In the modified Sartorius score the number of affected body sites contributes significantly to the final severity score.[11] However, a previous study did not demonstrate a difference in Sartorius score between patients with onset before the age of 16 (n=80), onset between 17-27 years (n=149) and onset after 28 years (n=67).[11]

We found that early-onset patients were more often nonsmokers or began smoking after the onset of HS, whereas most normal-onset patients had smoked before they developed symptoms. Possibly, early-onset patients were discouraged from starting to smoke because it could worsen HS.[4]

A limitation of our study is that the age of onset was based on patient-reported information. Further, the cutoff point for early-onset disease was based on general pubertal age in the Netherlands.[8] Establishing the pubertal status objectively for every individual patient would be preferable, but is not feasible in practice, because the "time to diagnosis" is notoriously long in HS.[1,13] A third limitation is that the Hurley score was used to assess disease severity.

In conclusion, early-onset HS occurred in almost 8% of our HS patients, and was associated with a family history of HS in 56% and a more widespread disease. Patients with early-onset HS should be closely monitored and receive appropriate treatments. However, it remains to be determined whether early treatments prevent progression of HS.

ACKNOWLEDGEMENTS

The authors thank Duco G. van den Broecke for the data from patients treated at the Department of Plastic Surgery of the Diaconessenhuis, Leiden; and Caspar W.N. Looman for support in the statistical analyses.

REFERENCES

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

2 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

3 Canoui-Poitrine F, Le Thuaut A, Revuz JE, *et al.* Identification of three hidradenitis suppurativa phenotypes: Latent class analysis of a cross-sectional study. *J Invest Dermatol* 2013; **133**: 1506–1511.

4 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

5 Schrader AMR, Deckers IE, van der Zee HH, *et al.* Hidradenitis suppurativa: A retrospective study of 846 Dutch patients to identify factors associated with disease severity. *J Am Acad Dermatol* 2014; **71**: 460–467.

6 Mengesha YM, Holcombe TC, Hansen RC. Prepubertal hidradenitis suppurativa: two case reports and review of the literature. *Pediatr Dermatol* 1999; **16**: 292–296.

7 Palmer RA, Keefe M. Early-onset hidradenitis suppurativa. *Clin Exp Dermatol* 2001; **26**: 501–503.

8 Talma H, Schönbeck Y, van Dommelen P, *et al.* Trends in menarcheal age between 1955 and 2009 in the Netherlands. *PLoS One* 2013; **8**: e60056.

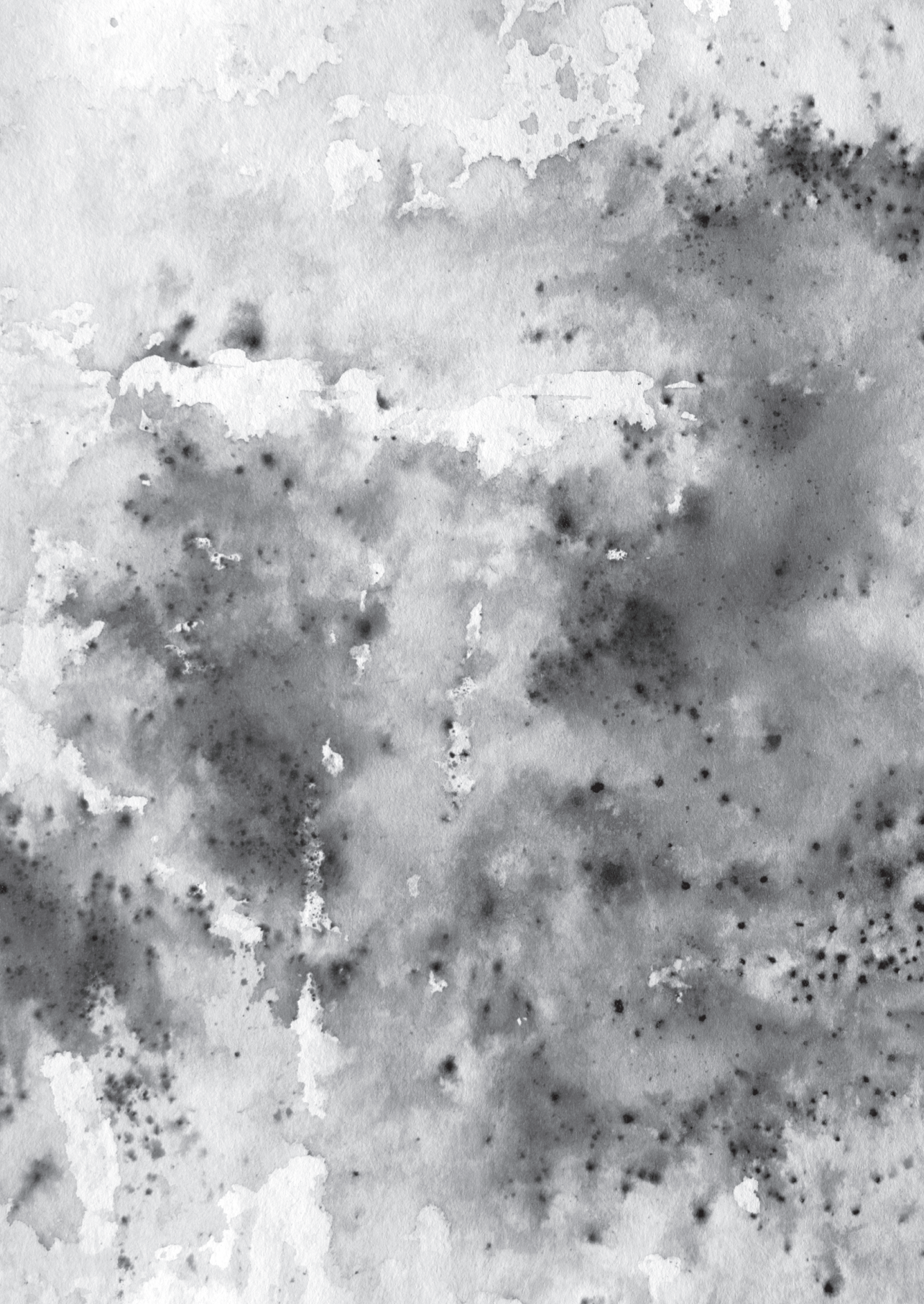
9 Garmhausen D, Hagemann T, Bieber T, *et al.* Characterization of different courses of atopic dermatitis in adolescent and adult patients. *Allergy* 2013; **68**: 498–506.

10 Stuart P, Malick F, Nair RP, *et al.* Analysis of phenotypic variation in psoriasis as a function of age at onset and family history. *Arch Dermatol Res* 2002; **294**: 207–213.

11 Canoui-Poitrine F, Revuz JE, Wolkenstein P, *et al.* Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. *J Am Acad Dermatol* 2009; **61**: 51–57.

12 Von der Werth JM, Williams HC. The natural history of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2000; **14**: 389–392.

13 Van der Zee HH, Laman JD, Boer J, Prens EP. Hidradenitis suppurativa: viewpoint on clinical phenotyping, pathogenesis and novel treatments. *Exp Dermatol* 2012; **21**: 735–739.



Chapter 3

Hidradenitis suppurativa: a retrospective study of 846 Dutch patients to identify factors associated with disease severity

Anne M.R. Schrader, Inge E. Deckers,
Hessel H. van der Zee, Jurr Boer, Errol P. Prens

J Am Acad Dermatol. 2014;71:460-467

ABSTRACT

Background: Few comprehensive studies exist on the epidemiology of hidradenitis suppurativa (HS), a very distressing skin disease.

Objective: We sought to identify disease-related factors associated with severity, sex, and family history.

Methods: Ordinal logistic regression was used in 846 consecutive Dutch patients with HS to calculate odds ratios (ORs) for severity according to Hurley. Sex and family history were compared using Student's *t*-test and chi-square test.

Results: In total, 45.5% of the patients had Hurley I, 41.5% had Hurley II, and 13.0% had Hurley III. Severity was associated with male sex (OR 2.11; $P < 0.001$), disease duration (OR 1.03; $P < 0.001$), body mass index (OR 1.03; $P = 0.01$), smoking pack-years (OR 1.02; $P = 0.001$), and axillary (OR 2.24; $P < 0.001$), perianal (OR 1.92; $P < 0.001$) and mammary lesions (OR 1.48; $P = 0.03$). Women had earlier onset, more inguinal and mammary lesions, and more frequent family history of HS. Men more commonly had gluteal, perianal and atypical lesions, and a history of severe acne. Patients with a family history had earlier onset, longer disease duration, a history of severe acne, more extensive disease, and were more often smokers.

Limitations: Some parameters were patient-reported.

Conclusion: The severity risk factors identified in this study could help physicians to select patients who need close monitoring and who would benefit from early, aggressive therapy.

INTRODUCTION

Hidradenitis suppurativa (HS) (or acne inversa) is a chronic inflammatory skin disease that presents with recurrent, painful deep-seated nodules or abscesses in the inverse areas of the body, usually the axillary, inguinal and anogenital regions.[1] It is highly distressing and has a large impact on quality of life.[2–4] Estimated prevalence rates in the Western world range between 1% and 4%.[5] The disease generally develops in the early twenties.[6,7] Disease-associated factors are female sex, a family history, cigarette smoking, and obesity.[5,8,9]

Because to its chronic and recurrent nature, HS is notoriously difficult to treat. Treatment options include topical and systemic antibiotics as well as immunomodulating drugs such as anti-tumor necrosis factor alpha biologics. In addition, surgical excision with secondary healing is often necessary. Although wide surgical excision is considered to be the only curative option,[10–13] it can have a major negative impact on patients with severe and extensive disease.

Because few comprehensive epidemiological studies have been conducted, it cannot be currently predicted which patients will progress to severe HS. We therefore used the disease characteristics of 846 patients with HS in The Netherlands to determine risk factors for HS severity. These factors might serve as a tool for identifying patients at risk for developing severe disease. In these patients, rapid and adequate treatment might prevent disease aggravation and reduce the future burden of this devastating disease. We also determined the differences in disease characteristics between males and females, and between positive and negative family histories. Greater knowledge of disease-specific characteristics would help physicians to better understand HS and to better inform their patients.

METHODS

Between 2007 and 2013, we collected data from all consecutive patients with HS referred to three Dutch clinics with a special interest in HS: the Department of Dermatology at Erasmus Medical Center, Rotterdam; the Department of Dermatology at Deventer Hospital, Deventer; and the Department of Plastic Surgery at Diaconessenhuis, Leiden. The respective diagnoses of HS in these hospitals were made by one of the authors or Duco G. van den Broecke, MD, (Department of Plastic Surgery, Diaconessenhuis, Leiden, The Netherlands) on the basis of a patient's history of HS symptoms, and of physical examination, as described by Revuz.[1]

Disease severity was staged according to Hurley.[14] Hurley stage I is limited to single or multiple abscesses without sinus tracts or scarring. Stage II consists of widely separated

single or multiple recurrent abscesses with sinus-tract formation and scarring. Hurley III is present when an entire area is diffusely involved with multiple interconnected tracts.

Patient characteristics were collected from medical files. A positive family history was assumed if patients reported first- or second-degree relatives with HS symptoms. Typical lesions in regions other than the predisposed HS regions were classified as atypical. The axillary, inguinal, femoral, perianal, genital, gluteal, abdominal, and mammary (i.e. mammary and inframammary) regions were considered as predisposed HS regions. For this type of retrospective investigation, no medical ethical committee approval is required under Dutch law.

Statistical analyses

First, we described the patient characteristics for the overall study population and for the individual Hurley stages. Second, to identify severity risk factors, we tested the patient characteristics for significant odds ratios (ORs) across the Hurley stages. Third, we compared the patients' characteristics based on sex and family history. Patient characteristics were presented using descriptive statistics with continuous data as mean ± standard deviation (SD) and categorical data as number (%). Severity risk factors were determined using univariable and multivariable ordinal logistic regression models.

These statistics were the most suitable, since the Hurley classification -the dependent variable- has more than two response categories that represent a rank order. The models also assume that predictors -the patient characteristics- are linearly related to the log odds of the Hurley stages. This was tested with a nonsignificant test of parallel lines, indicating that the odds are proportional.

Proportional ORs were obtained on the three levels of the Hurley stages, which should be interpreted as follows: a significant OR of 2 indicates that the odds of Hurley II and III combined versus Hurley I are twice as high for that factor. Likewise, the odds of Hurley III versus Hurley I and II combined are also twice as high. Patient characteristics for sex and a family history were compared using Student's *t*-test for continuous data and chi-square test for categorical data. For statistical analyses, we used SPSS Statistics 20 (IBM Corp, Armonk, NY). A two-sided *P*-value of less than 0.05 was considered statistically significant. For the categorical data, an OR of less than 5% (0.95-1.05) was interpreted as not clinically relevant.

RESULTS

A total of 846 HS patients were seen, 410 at Erasmus Medical Center, 404 at Deventer Hospital, and 32 at Diaconessenhuis, and were included and analyzed (Table I). The mean age was 38.0 ± 12.7 years, with a mean disease duration of 13.8 ± 11.0 years. The

Table I. Patient characteristics

	Hurley I n=385 (45.5%)	**Hurley II** n=351 (41.5%)	**Hurley III** n=110 (13.0%)	**Total** n=846
Sex, n (%)				
- Female	310 (80.5)	245 (69.8)	59 (53.6)	614 (72.6)
- Male	75 (19.5)	106 (30.2)	51 (46.4)	232 (27.4)
Age of disease onset years, mean ± SD; n=839	24.2 ± 11.6	24.1 ± 11.0	24.5 ± 10.5	24.2 ± 11.2
Disease duration years, mean ± SD; n=839	11.2 ± 10.2	15.3 ± 10.9	18.1 ± 11.7	13.8 ± 11.0
BMI kg/m^2, mean ± SD; n=813	27.6 ± 6.1	28.5 ± 5.9	28.9 ± 7.0	28.1 ± 6.1
BMI subgroups, n (%)[a]				
- Normal weight	156 (41.4)	104 (31.1)	34 (33.7)	294 (36.2)
- Overweight	104 (27.6)	119 (35.5)	33 (32.6)	256 (31.5)
- Obese	117 (31.0)	112 (33.4)	34 (33.7)	263 (32.3)
- Unknown	8	16	9	33
Smoking status, n (%)				
- Nonsmoker	72 (18.8)	42 (12.1)	13 (11.8)	127 (15.1)
- Current smoker	260 (67.9)	260 (74.7)	75 (68.2)	595 (70.7)
- Ex-smoker	51 (13.3)	46 (13.2)	22 (20.0)	119 (14.2)
- Unknown	2	3	-	5
Pack years (ex-)smokers, mean ± SD; n=665	15.5 ± 12.7	19.3 ± 13.2	27.9 ± 24.5	18.8 ± 15.6
Family history of HS, n (%)				
- Yes	139 (37.3)	109 (33.1)	35 (36.5)	283 (35.5)
- Unknown	12	22	14	48
History of severe acne vulgaris, n (%)				
- Yes	68 (23.1)	64 (26.3)	21 (24.4)	153 (24.6)
- Unknown	91	108	24	233
Co-occurrence of DM, n (%)				
- Yes	17 (5.2)	16 (5.8)	14 (16.1)	47 (6.8)
- Unknown	55	75	23	153
Affected regions, n (%)				
- Axillary	201 (54.8)	241 (69.3)	90 (81.8)	541 (64.3)
- Inguinal	320 (83.6)	287 (82.5)	95 (86.4)	702 (83.5)
- Femoral	86 (22.5)	79 (23.0)	20 (18.5)	185 (22.2)
- Perianal	51 (13.3)	69 (19.8)	38 (34.5)	158 (18.8)
- Genital	97 (25.3)	99 (28.8)	31 (28.4)	227 (27.2)
- Gluteal	142 (37.1)	148 (42.5)	60 (54.5)	350 (41.6)
- Abdomen	52 (13.6)	65 (18.7)	25 (22.7)	142 (16.9)
- Mammary	61 (15.9)	90 (25.9)	24 (22.0)	175 (20.8)
- Atypical	48 (12.5)	54 (15.4)	23 (20.9)	125 (14.8)
- Unknown	2	7	2	11

BMI - body mass index; DM - diabetes mellitus; HS - hidradenitis suppurativa

[a] Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

majority of patients were female (72.6%). Approximately one-third had a normal weight (36.2%), one third were overweight (31.5%) and another third were obese (32.3%). The overall body mass index (BMI) was 28.1 ± 6.1. A majority was current cigarette smokers (70.7%) or ex-cigarette smokers (14.2%); only 15.1% were nonsmokers. About one third (35.5%) reported a family history. The body regions most commonly affected were the inguinal (83.5%), axillary (64.3%) and gluteal (41.6%) regions. In a quarter of the patients, the genital, and femoral areas were involved, followed by the mammary, perianal and abdominal region. The least affected body regions were the atypical regions (14.8%). A history of severe acne was reported by 24.6% of the patients, and co-occurrence of diabetes mellitus (DM) by 6.8%.

The strongest severity risk factors are male sex, and axillary and perianal involvement

Whereas 13.0% of the patients had Hurley III, the percentages with Hurley I (45.5%) and Hurley II (41.5%) were similar (Table I). Table II presents the outcomes of the ordinal logistic regression models. The majority of the study population was female, with a female:male ratio of 2.6:1. This ratio decreased from 4.1:1 in Hurley I, to 2.3:1 in Hurley II, and to 1.2:1 in Hurley III, indicating that males are more at risk for developing severe disease. This was confirmed by a significant proportional OR of 2.11 ($P < 0.001$).

Disease duration was longer in severe disease, increasing from 11.2 years in Hurley I, to 15.3 years in Hurley II, and to 18.1 years in Hurley III, with a significant OR of 1.03 for each additional disease year ($P < 0.001$). BMI (Hurley I 27.6, Hurley II 28.5, and Hurley III 28.9) was identified as a severity risk factor, with an OR of 1.03 per BMI unit increase ($P = 0.01$).

As the calculated pack-years were higher in patients with more severe disease (15.5 in Hurley I, 19.3 in Hurley II, and 27.9 in Hurley III), they were identified as a severity risk factor, with a significant OR of 1.02 per added pack year ($P = 0.001$). Fewer patients with Hurley I were current or ex-smokers (81.2%) than Hurley II (87.9%) and Hurley III (88.2%). In the univariable analysis, but not in the multivariable analysis, smoking status had significant ORs across the Hurley stages.

In severe disease, more body regions were affected. The percentage of patients with affected axillae increased the most, from 54.8% in Hurley I, to 69.3% in Hurley II, and to 81.8% Hurley III, with a significant OR of 2.24 ($P < 0.001$). Two more body regions were associated with HS severity: the perianal region, with an OR of 1.92 ($P < 0.001$), and the mammary region, with an OR of 1.48 ($P = 0.03$). In the univariable analysis, but not in the multivariable analysis, the gluteal, abdominal and atypical areas had significant ORs across the Hurley stages.

Because there was no difference in mean age of disease onset (24.2 years in Hurley I, 24.1 years in Hurley II, and 24.5 years in Hurley III) and in having a family history of HS (37.3% Hurley I, 33.1% Hurley II, and 36.5% Hurley III), there was no significant difference

in the OR. Neither did a history of severe acne influence disease severity. A history of severe acne was reported by 26.3% of the patients with Hurley II, against 23.1% of Hurley I and 24.4% in Hurley III. At 16.1%, co-occurrence of DM was highest in Hurley III, decreasing to 5.8% in Hurley II and 5.2% in Hurley I. The OR was significant in the univariable analysis (OR 2.25, $P = 0.004$) but not in the multivariable analysis.

Table II. Risk factors for disease severity

Model 1[a]	**Univariable** (n=846)		**Multivariable** (n=846)	
	OR (95%CI)	***P*-value**[c]	**OR (95%CI)**	***P*-value**[c]
Sex, ref. female				
- Male	2.28 (1.71-3.05)	**<0.001**	2.11 (1.54-2.89)	**<0.001**
Age of disease onset years	1.00 (0.99-1.01)	0.92	1.00 (0.98-1.01)	0.73
Disease duration years	1.04 (1.03-1.06)	**<0.001**	1.03 (1.02-1.05)	**<0.001**
BMI	1.03 (1.01-1.05)	**0.01**	1.03 (1.01-1.05)	**0.01**
Smoking status, ref. nonsmoker				
- Current smoker	1.60 (1.10-2.33)	**0.01**	0.94 (0.60-1.47)	0.78
- Ex-smoker	1.86 (1.15-3.01)	**0.01**	1.14 (0.64-2.02)	0.66
Pack years	1.03 (1.02-1.04)	**<0.001**	1.02 (1.01-1.03)	**0.001**
Family history of HS, ref. no	0.90 (0.68-1.18)	0.45	0.80 (0.58-1.09)	0.15
Model 2[b]	**Univariable** (n=846)		**Multivariable** (n=846)	
	OR (95%CI)	***P*-value**[c]	**OR (95%CI)**	***P*-value**[c]
History of severe acne vulgaris, ref. no	1.12 (0.80-1.58)	0.52	1.09 (0.74-1.59)	0.67
Co-occurrence of DM, ref. no	2.25 (1.29-3.93)	**0.004**	1.43 (0.77-2.68)	0 .26
Body region affected, ref. region not affected				
- Axillary	2.24 (1.70-2.96)	**<0.001**	2.24 (1.63-3.08)	**<0.001**
- Inguinal	1.05 (0.74-1.48)	0.80	1.05 (0.70-1.57)	0.81
- Femoral	0.92 (0.68-1.26)	0.62	0.90 (0.64-1.27)	0.56
- Perianal	2.21 (1.59-3.08)	**<0.001**	1.92 (1.34-2.76)	**<0.001**
- Genital	1.16 (0.87-1.55)	0.31	0.99 (0.72-1.36)	0.93
- Gluteal	1.50 (1.16-1.95)	**0.002**	1.19 (0.88-1.60)	0.26
- Abdominal	1.55 (1.11-2.19)	**0.01**	1.28 (0.86-1.89)	0.22
- Mammary	1.54 (1.12-2.10)	**0.01**	1.48 (1.03-2.11)	**0.03**
- Atypical	1.47 (1.03-2.10)	**0.04**	1.25 (0.85-1.84)	0.25

BMI - body mass index; CI - confidence interval; DM - diabetes mellitus; HS - hidradenitis suppurativa; OR - odds ratio; *ref.* - reference category

[a] Ordinal logistic regression analyses with the Hurley stages as dependent variable: univariable model, unadjusted; and multivariable model, adjusted for factors and covariates in model.

[b] Ordinal logistic regression analyses with the Hurley stages as dependent variable: univariable model, unadjusted; and multivariable model, adjusted for statistically significant factors and covariates of the multivariable model 1.

[c] *P*-value of ordinal logistic regression analyses.

Table III. Patient characteristics by sex

	Female 614 (72.6%)	**Male** 232 (27.4%)	***P*-value**[a]
Age of disease onset years, mean ± SD; n=839	23.5 ± 10.8	26.2 ± 12.1	**0.003**
Disease duration years, mean ± SD; n=839	13.9 ± 10.5	13.4 ± 12.2	0.61
BMI kg/m^2, mean ± SD; n=813	28.1 ± 6.3	28.0 ± 5.8	0.79
BMI subgroups, n (%)[b]			0.24
- Normal weight	217 (36.8)	77 (34.5)	
- Overweight	174 (29.5)	82 (36.8)	
- Obese	199 (33.7)	64 (28.7)	
- Unknown	24	9	
Smoking status, n (%)			0.08
- Nonsmoker	103 (16.9)	24 (10.4)	
- Current smoker	427 (70.0)	168 (72.7)	
- Ex-smoker	80 (13.1)	39 (16.9)	
- Unknown	4	1	
Pack years (ex-)smokers, mean ± SD; n=665	17.9 ± 13.8	21.1 ± 19.1	**0.03**
Family history of HS, n (%)			
- Yes	223 (38.4)	60 (27.6)	**0.02**
- Unknown	33	15	
History of severe acne vulgaris, n (%)			
- Yes	77 (17.6)	76 (40.9)	**<0.001**
- Unknown	177	46	
Co-occurrence of DM, n (%)			
- Yes	33 (6.7)	14 (7.1)	0.37
- Unknown	118	35	
Affected regions, n (%)			
- Axillary	385 (63.2)	156 (67.2)	0.21
- Inguinal	536 (88.0)	166 (71.6)	**<0.001**
- Femoral	125 (20.7)	60 (26.1)	0.19
- Perianal	91 (14.9)	67 (28.9)	**<0.001**
- Genital	173 (28.6)	54 (23.4)	0.15
- Gluteal	234 (38.4)	116 (50.0)	**0.004**
- Abdomen	101 (16.6)	41 (17.7)	0.36
- Mammary	148 (24.3)	27 (11.7)	**<0.001**
- Atypical	71 (11.6)	54 (23.3)	**<0.001**
- Unknown	9	2	

BMI - body mass index; DM - diabetes mellitus; HS - hidradenitis suppurativa

[a] *P*-value of Student's *t*-test for continuous and chi-square test for categorical data

[b] Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

Females develop HS at an earlier age and inguinal and mammary regions are more frequently involved

The patient characteristics by sex are presented in Table III. In general, HS is more common in females than in males (72.6% vs 27.4%). Mean age of disease onset was lower in women than in men (23.5 vs 26.2 years; $P = 0.003$). More females reported a family history of HS (38.4% vs 27.6%; $P = 0.02$) and a lower percentage reported a history of severe acne (17.6% vs 40.9%; $P < 0.001$). Although a higher percentage of women were nonsmokers (16.9% vs 10.4%; $P = 0.08$), this was not significant. Females, however, did have fewer pack-years than male patients (17.9 vs 21.1 pack-years; $P = 0.03$). BMI and co-occurrence of DM did not differ significantly. The predisposed areas for females were the inguinal region (88.0% vs 71.6%; $P < 0.001$), and mammary region (24.3% vs 11.7%; $P < 0.001$). Men more commonly had lesions in the gluteal (50.0% vs 38.4%; $P = 0.004$), perianal (28.9% vs 14.9%; $P < 0.001$) and atypical (23.3% vs 11.6%; $P < 0.001$) regions.

A positive family history leads to an earlier disease onset and more extensive disease, but not to more severe disease

Patients with a family history of HS (Table IV) were more often females (78.8% vs 69.5%; $P = 0.02$), had a lower mean age of disease onset (20.2 vs 26.2 years; $P < 0.001$), and had a longer disease duration (16.3 vs 12.4 years; $P < 0.001$). Fewer of them were nonsmokers (12.7% vs 17.0%; $P = 0.01$). Although a significantly higher percentage of patients with a family history reported a history of severe acne (28.6% vs 21.5%; $P < 0.001$), co-occurrence of DM was less common (5.4% vs 7.5%; $P < 0.001$). Except for the genital and atypical regions, all other areas were affected more frequently in patients with a family history ($P < 0.001$ - $P = 0.003$).

DISCUSSION

This analysis of 846 HS patients in The Netherlands determined five severity risk factors: male sex, obesity, smoking pack-years, disease duration, and lesions in the axillary, perianal and mammary regions.

Our finding of a higher risk of severe disease in males was previously suggested by Matusiak *et al.*[15] in 54 patients with HS, and more recently by Vazquez *et al.*[16] in 268 patients with HS. The outcome that obesity (measured as BMI) is a severity risk factor was in accordance with the results presented by Sartorius *et al.*[7] in 115 patients with HS, and with those presented by Canoui-Poitrine *et al.*[6] in 302 patients with HS. But while Vazquez *et al.*[16] and Sartorius *et al.*[7] also found that severe HS is associated with cigarette smoking in general, our results suggest that this is not the case. We found that smoking pack-years, in which the number of cigarettes and duration of smoking are taken

Table IV. Patient characteristics by family history of hidradenitis suppurativa

	Family history of HS 283 (35.5%)	**No family history of HS** 515 (64.5%)	***P*-value**[a]
Sex, n (%)			**0.02**
- Female	223 (78.8)	358 (69.5)	
- Male	60 (21.2)	157 (30.5)	
Age of disease onset years, mean ± SD; n=793	20.2 ± 8.8	26.2 ± 11.9	**<0.001**
Disease duration years, mean ± SD; n=793	16.3 ± 11.2	12.4 ± 10.6	**<0.001**
BMI kg/m^2, mean ± SD; n=769	28.4 ± 6.6	28.1 ± 5.9	0.51
BMI subgroups, n (%)[b]			0.06
- Normal weight	103 (37.3)	170 (34.5)	
- Overweight	74 (26.8)	168 (34.1)	
- Obese	99 (35.9)	155 (31.4)	
- Unknown	7	22	
Smoking status, n (%)			**0.01**
- Nonsmoker	36 (12.7)	87 (17.0)	
- Current smoker	207 (73.1)	345 (67.5)	
- Ex-smoker	40 (14.1)	79 (15.5)	
- Unknown	-	4	
Pack years (ex-)smokers, mean ± SD; n=570	18.0 ± 13.6	19.1 ± 16.7	0.40
History of severe acne vulgaris, n (%)			
- Yes	68 (28.6)	81 (21.5)	**<0.001**
- Unknown	45	139	
Co-occurrence of DM, n (%)			
- Yes	14 (5.4)	32 (7.5)	**<0.001**
- Unknown	25	91	
Affected regions, n (%)			
- Axillary	199 (70.3)	323 (63.1)	**<0.001**
- Inguinal	258 (91.2)	408 (79.7)	**<0.001**
- Femoral	73 (25.9)	110 (21.7)	**0.003**
- Perianal	69 (24.4)	87 (17.0)	**<0.001**
- Genital	77 (27.3)	135 (26.6)	0.18
- Gluteal	151 (53.4)	187 (36.5)	**<0.001**
- Abdomen	62 (21.9)	76 (14.8)	**<0.001**
- Mammary	69 (24.4)	104 (20.3)	**<0.001**
- Atypical	44 (15.5)	77 (15.0)	0.06
- Unknown	1	8	

BMI - body mass index; DM - diabetes mellitus; HS - hidradenitis suppurativa.

[a] *P*-value of Student *t*-test for continuous and chi-square test for categorical data.

[b] Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

into account, were of influence on disease severity. Although, among other factors, smoking pack-years were adjusted for disease duration in the multivariable analysis, a higher number of pack-years can only accumulate over time. As a severity risk factor that has never been reported, we identified longer disease duration. These two factors, smoking pack-years and longer disease duration, both suggest that time is a substantial factor in the development of severe HS. The final severity risk factor that we identified was disease involvement of the axillary, perianal and mammary regions. Although the axillary and inguinal were most commonly affected, involvement of the axillary region only increased significantly in more severe disease. This supports axillary involvement as a severity risk factor. The only body sites previously reported to be associated with disease severity were the atypical locations.[6] Furthermore, our study did not confirm the previously suggested relation between a history of severe acne and severe HS.[7]

In general, HS is associated with female sex.[5] Our finding that 72.6% of patients with HS were female is consistent with previous estimates, which ranged from 70.5% to 86%.[6–8,16] In addition, our results not only suggest that males have more severe disease, but also that HS manifests earlier in females, that females more often report a family history, that more males have a history of severe acne, and that different body regions were involved in males than in females. Men had more lesions in the gluteal, perianal, and atypical regions, and women had more lesions in the inguinal, and mammary areas. This is in agreement with Canoui-Poitrine *et al.*[6] who stated that "the front part of the body was predominantly involved in female patients, whereas involvement of the back of the body was a hallmark of male patients. "Although predisposition of females for the mammary region can be expected, involvement of this region was not uncommon in males.

There is currently a lively discussion on whether or not there is a genetic predisposition to HS. In our study, a family history of HS was reported in more than a third of our patients, which is similar to the percentages of 35.5% and 38% described.[6,7] Previously, it was only reported that earlier disease onset was associated with a family history of HS.[6] Our results add that, in patients with a family history of HS, the disease developed earlier and lasted longer, more patients were female, were smokers or ex-smokers, a higher percentage had severe acne, and almost all body areas were affected more often.

Our finding that 13.0% of the patients had Hurley III is higher than previously reported in a hospital setting (3.9%)[6] and population-based (2.2%),[16] but lower than in patients qualifying for surgical intervention (22.2%).[15] The most likely explanation for this is that our clinics are mainly tertiary referral centers. The rates we observed of 45.5% Hurley I, and 41.5% Hurley II lie in the percentages reported in previous studies, which ranged from 24.1% to 68.2% for Hurley I and 27.6% to 53.7% for Hurley II.[6,15,16]

To our knowledge, this study represents the largest HS population studied to date. Only experienced physicians classified disease severity in all patients according to Hurley. Because the study population comprised a substantial number of patients with

severe disease, it enabled us to use tailored statistics to identify severity risk factors. A limitation of the study is that part of the data was self-reported (age of disease onset, family history, co-occurrence of DM, history of severe acne, and smoking status).

In conclusion, while we have demonstrated that HS severity is associated with male sex, obesity, smoking pack-years, disease duration, and involvement of axillary, perianal and mammary regions, it is not associated with age of disease onset, a family history of HS, history of severe acne, or co-occurrence of DM. These severity risk factors could serve as a tool to identify young patients with HS at risk, and should alert the physician to the need to monitor these patients closely and to start earlier with aggressive surgery or pharmaceutical therapies.

ACKNOWLEDGEMENTS

The authors thank Duco G. van den Broecke for the data from the patients with HS treated at the Department of Plastic Surgery of the Diaconessenhuis, Leiden; Loes M. Hollestein for support in the statistical analyses; and Jon D. Laman and David Alexander for their critical readings of the manuscript.

REFERENCES

1 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

2 Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol* 2010; **90**: 264–268.

3 Esmann S, Jemec GB. Psychosocial impact of hidradenitis suppurativa: a qualitative study. *Acta Derm Venereol* 2011; **91**: 328–332.

4 Onderdijk AJ, van der Zee HH, Esmann S, *et al.* Depression in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2013; **27**: 473–478.

5 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

6 Canoui-Poitrine F, Revuz JE, Wolkenstein P, *et al.* Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. *J Am Acad Dermatol* 2009; **61**: 51–57.

7 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

8 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

9 König A, Lehmann C, Rompel R, Happle R. Cigarette smoking as a triggering factor of hidradenitis suppurativa. *Dermatology* 1999; **198**: 261–264.

10 Ritz JP, Runkel N, Haier J, Buhr HJ. Extent of surgery and recurrence rate of hidradenitis suppurativa. *Int J Colorectal Dis* 1998; **13**: 164–168.

11 van der Zee HH, Prens EP, Boer J. Deroofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. *J Am Acad Dermatol* 2010; **63**: 475–480.

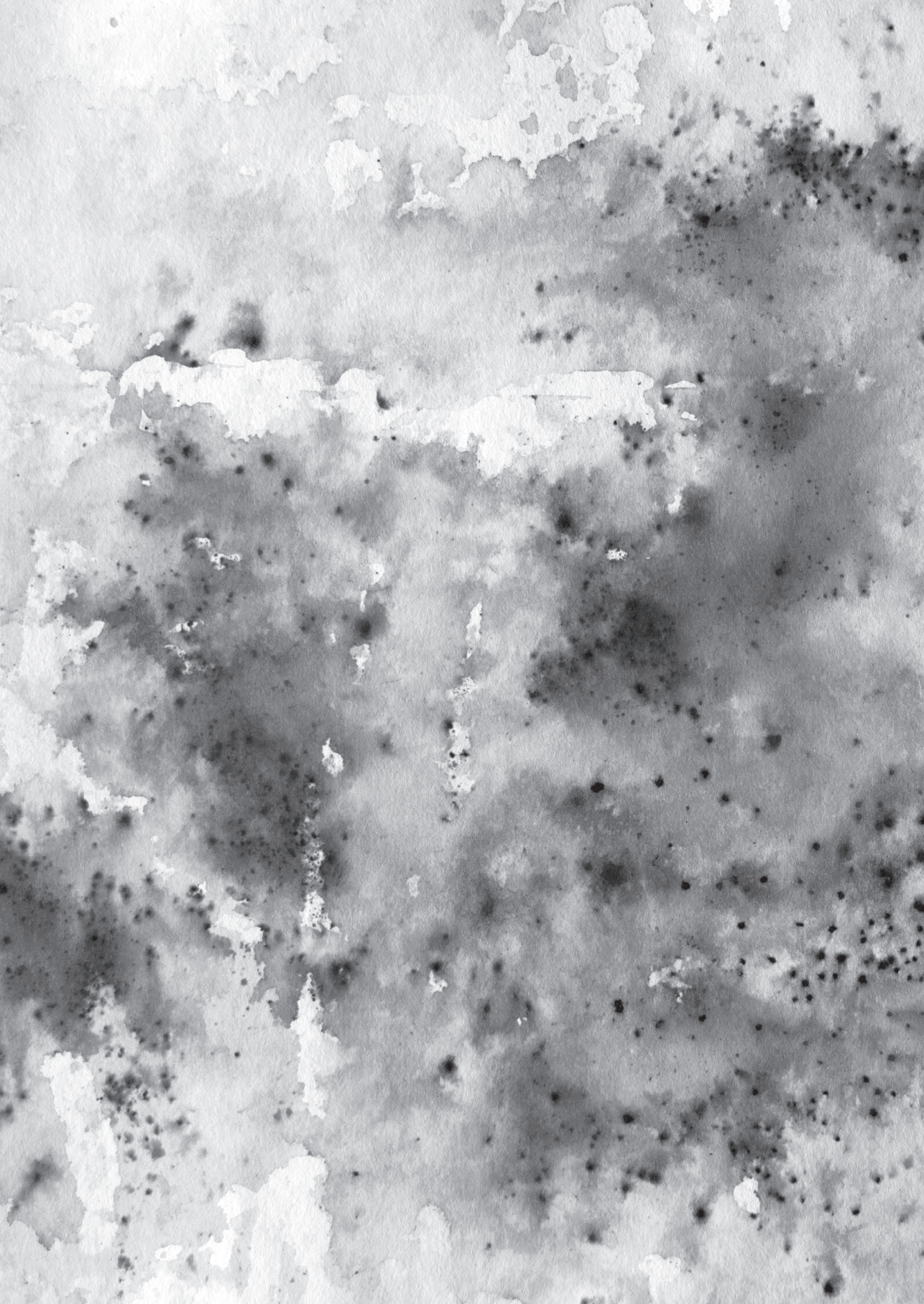
12 Hattem S, Spoo JR, Horváth B, *et al.* Surgical treatment of sinuses by deroofing in hidradenitis suppurativa. *Dermatol Surg* 2012; **38**: 494–497.

13 Ellis LZ. Hidradenitis suppurativa: Surgical and other management techniques. *Dermatol Surg* 2012; **38**: 517–536.

14 Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. In Roenigh RRH (eds). *Dermatologic Surgery.* Marcel Dekker, New York.1989; 729–739.

15 Matusiak Ł, Bieniek A, Szepietowski JC. Hidradenitis suppurativa and associated factors: still unsolved problems. *J Am Acad Dermatol* 2009; **61**: 362–365.

16 Vazquez BG, Alikhan A, Weaver AL, *et al.* Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol* 2013; **133**: 97–103.



Chapter 4

Risk factors, clinical course and long-term prognosis in hidradenitis suppurativa: a cross-sectional study

Charles B. Kromann*, Inge E. Deckers*, Solveig Esmann, Jurr Boer, Errol P. Prens, Gregor B.E. Jemec

*Shared first authors

Br J Dermatol. 2014;171:819-824

ABSTRACT

Background: Hidradenitis suppurativa (HS) causes considerable morbidity. The long-term prognosis is of obvious interest to both patients and physicians. We conducted this study to determine the prognosis and risk factors in patients diagnosed with HS.

Objective: To describe the long-term prognosis and the clinical course of HS and its association to known risk factors.

Methods: A postal follow-up survey with uncomplicated factual questions was conducted. As all the patients were well acquainted with their long-standing disease, this was thought to be sufficient for meaningful results. All cases were diagnosed by a dermatologist. Overall, 212 patients diagnosed with HS between 1981 and 2001 were studied after a median follow-up period of 22 years (range 12-32).

Results: The overall response rate was 71.2%, with 60.8% (129/212) valid (fully completed) questionnaires. Remission was reported by 39.4% (50/127) and improvement by 31.5% (40/127). Unchanged severity was reported by 20.5% (26/127) and 8.7% (11/127) experienced disease worsening. Tobacco smoking was reported by 92.2% (119/129). Among nonsmokers, 48.5% (33/68) reported remission versus 28.8% (17/59) of active smokers. A higher proportion of nonobese patients (44.8%, 43/96) reported remission than obese patients (22.6%, 7/31).

Conclusions: We found that 39.4% of the sample reported remission of HS. Suspected risk factors appeared to influence the prognosis. Smoking and obesity were significantly linked to a lower rate of self-reported remission. The notion that lifestyle factors play a role in HS appears to be supported by this survey.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurring, debilitating skin disease of the hair follicles. It usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal and anogenital regions (Dessau definition, first International Conference on Hidradenitis Suppurativa/Acne Inversa, 30 March to 1 April 2006, Dessau, Germany).[1,2] It follows from this definition that HS is likely to have a major impact on the lives of patients, a suggestion that is supported by the therapeutic challenges presented by HS. Encouragingly, therapy is currently attracting renewed attention owing to new treatment opportunities.[3] Data on the prognosis or the natural evolution of the disease are nevertheless of great interest to all those involved.

Although long-term follow-up is common for malignant skin disease,[4] knowledge of the natural course of most benign dermatological diseases remains sporadic, and the prognosis of only a few diseases has been systematically explored.[5–8] Knowledge about the natural course of HS is limited to sporadic accounts and a paper from von der Werth and Williams.[9] Their study was based on patients undergoing treatment at the Department of Dermatology in Nottingham, U.K., and revealed interesting data regarding age of onset, disease duration, possible remission, family history, aggravating factors and the effects of menstrual cycle and menopause on women with HS.[9]

Subsequently, obesity and tobacco smoking have been identified as additional risk factors.[10–14] Both factors have been linked to clinical disease severity,[15] and it has been suggested that weight reduction in the obese may ameliorate HS.[16,17] It has furthermore been implied that HS symptoms ameliorate spontaneously with age,[9] and that some patients can become disease-free over time.[18] However, data are limited.

We have therefore conducted a long-term follow-up of patients diagnosed with HS, but not necessarily subsequently treated at our institutions, in order to describe the clinical course of HS in greater detail.

PATIENTS AND METHODS

Study design

A postal questionnaire based long-term follow-up study with simple factual questions was conducted, partly of retrospective character and partly of current relevance. All patients were initially diagnosed by a dermatologist, and the clear symptomatology and long experience of the patients polled was thought to provide data of acceptable quality. To increase response rates, nonrespondents were either sent reminders by mail of telephoned.

Participants

Eligible patients (n=212) in two cohorts were identified: one Danish (n=141) and one Dutch (n=79). Patients were diagnosed with HS between 1981 and 2001, and identified through medical records. Patients were excluded when contact information was not available (n=7) or if they had died (n=13). Current contact details were retrieved in the host countries' social security number systems, or the addresses were looked up in medical records and cross-checked with public telephone books. There were 26 male and 186 female patients in the combined cohort (12.3% male), and the mean age was 52.1 years [95% confidence interval (CI) 50.8-53.2] at follow-up. The follow-up period was 12-32 years, with a median of 22 years.

Eligibility criteria and questionnaire

Patients were eligible if they had been diagnosed with HS by a qualified dermatologist and had a diagnosis recorded in their medical records. A seven-page, 43-question questionnaire was mailed to the 212 eligible participants, with a paid-postage return envelope enclosed. Questions regarding primary outcome measures such as development of disease, smoking, weight/height and family history were considered central. Questionnaires were counted as complete when 80% of central questions and 50% of other questions were answered. HS has easily identifiable symptoms, and patients who were diagnosed with HS by a dermatologist were considered able to answer simple and factual questions regarding the evolution of their disease.[19] A medical language expert and back translation was used ensuring the best possible conformity in the questionnaire in English, Danish and Dutch. No ethical approval for this study was necessary according Danish and Dutch law regarding the questionnaire. All data were anonymized before analysis.

Outcome measures

The outcome measures were basic data regarding remission, factors associated with remission and known risk factors. Self-reported remission (i.e. no inflammatory boils the last 6 months) was considered the primary endpoint, and used in comparisons where possible. Regarding prognostic factors we chose dichotomous categorical measures: active smoking versus nonsmoking, obesity [body mass index (BMI) > 30] versus nonobesity and family history versus no family history. The obesity versus nonobesity categorization was based on our recent study of morbidly obese experiencing amelioration of HS due to weight loss after bariatric surgery.[16]

Statistics

Unless otherwise noted, all statistic calculations were performed using SPSS Statistics version 20 (IBM, Armonk, NY, U.S.A.) for Mac OS X. Results are presented as a percentage,

or as a mean with a 95% CI or standard deviation (SD) where relevant. Comparing means was done assuming normal distribution where acceptable (n≈50) and using relevant parametric tests (*t*-test or ANOVA). Regarding prognostic factors for remission, multivariate analysis was done by logistic regression. With remission as the dependent, we controlled for categorical factors (active smoking, obesity, sex and familial disposition for HS) and age as a continuous variable. Point prevalence for the samples are reported with 95% CIs. Rates were compared using chi-square test using 2 x 2 cross tabulation if possible. In all comparisons $P < 0.05$ was considered significant. Effect size (ES) was calculated by hand as bias-corrected (Hedges) Cohen's *d*, and was reported as either small, medium or large according to Hojat and Xu.[20]

RESULTS

There was a response from 71.4% of the patients, yielding 60.8% (129/212) complete questionnaires. Incomplete questionnaires were scrutinized and excluded if found to be < 50% complete. The nonrespondents (28.8%) and participants denying ever having had a diagnosis of HS (10.4%) amounted to 39.2% (83/212). No differences were found between the Danish and Dutch cohorts for basic characteristics such as age or sex.

Among the valid respondents (n=129) there were 13 men and 116 women (10.1% male). Respondents were aged 30-86 years (mean 53.7 years, 95% CI 52.3-55.3) (Table I). Their BMI ranged from 18.3 to 48.0 kg/m^2 (mean 27.0, 95% CI 26.1-27.9). The year of diagnosis was in the range 1981-2001 and median was 1990; hence, the shortest follow-up period was 12 years, the longest period was 32 years and the median and average follow-up period was 22 years. Generally, nonrespondents were younger than respondents, with a mean age of 49.4 years (95% CI 47.6-51.4). In comparison with responders the mean difference of 4.3 years was significant ($P = 0.001$); however, the ES was only small to medium (ES 0.4). The male-to-female ratio was 13:70 (16% male) (Table I). There was no significant difference in this ratio compared with responders.

Table I. Respondent versus nonrespondent characteristics

	Respondents	Nonrespondents	Whole cohort
Number of patients (%)	129 (60.8)	83 (39.2)	212 (100)
Age years, mean (95% CI)	53.7 (52.3-55.3)	49.4 (47.6-51.4)	52.1 (50.8-53.2)
Male, n (%)	13 (10.1)	13 (15.7)	26 (12.3)
Female, n (%)	116 (89.9)	70 (84.3)	186 (87.7)

CI - confidence interval

Disease characteristics in respondents

In the cohort, 38.0% of patients (49/129) had a family history of HS defined as an affected first- or second-degree relative. Approximately two-fifths of respondents (41.9%, 54/129) indicated no familial disposition to HS, and 20.2% (26/129) registered their familial disposition as unknown. Symptomatic lesions were most frequently located in the groin (47.2%, 60/127) or genital area (29.9%, 38/127). Lesions in axillae were reported by 25.6% of patients (32/125) and inframammary lesions by 12.0% (15/125). More than one-third of the sample (33.9%, 43/127) had more than one affected region. Scarring was reported by 77.9% (67/86) of the respondents.

In describing the development of their disease, remission was reported by 39.4% of patients (50/127) and improvement by 31.5% (40/127). Only 20.5% (26/127) considered their disease severity to be unchanged, and 8.7% (11/127) indicated that their disease had worsened over time. Patients reporting remission were generally older; their mean age of achieving remission was 55.8 years (95% CI 53.4-58.3). Patients who reported active disease had a mean age of 52.4 years (95% CI 50.3-54.5). The mean difference -3.5 years ($P = 0.036$, ES 0.4). In general, once a region was affected it remained so. This was reported by 64.1% (66/103) of patients, whereas 33.0% (34/103) experienced activity in both established and new locations. Only 2.9% (three of 103) experienced total resolution in one location and activity in a new location. Within the group of participants reporting cessation of disease activity (39.4%, 50/127), the age of disease resolution was 23-69 years, with a mean of 41.8 years (95% CI 38.7-45.0). Among patients indicating that they still suffered from active HS, 43.8% (32/73) reported symptoms a few times a year; 31.5% (23/73) monthly symptoms, 4.1% (three of 73) symptoms every week and 20.6% (15/73) continuous activity.

The effect of pregnancy and menopause

The majority of women (71.8%, 61/85) reported no effect of pregnancy on their HS, while 20.0% (17/85) indicated amelioration and 8.2% (seven of 85) deterioration. Considering the influence of menopause on disease evolution, the majority of women (47.5%, 29/61) reported that menopause attenuated their symptoms. Some 37.7% (23/61) felt no difference after menopause and 14.8% (9/61) indicated worsening of their HS following menopause.

Risk factors and comorbidities

The lifelong incidence of tobacco smoking was 92.2% (119/129). In this sample 45.7% (59/129) were still active smokers, whereas 46.5% (60/129) reported having stopped smoking and 7.8% (10/129) had never smoked. The most prevalent self-reported comorbidities were hypertension, acne and diabetes; however, the sample generally had a high prevalence of comorbidities, which are listed in Table II.

Table II. Self-reported prevalence of comorbidities in sample

	Total cohort, x/n[a] (%)	**Age,** mean ± SD	**Male,** x/n[a] (%)	**Female,** x/n[a] (%)	**BMI,** mean ± SD
Hypertension	35/126 (27.8)	58.7 ± 8.8	3/13 (23)	32/113 (28)	28.5 ± 6.0
Facial acne	30/126 (23.8)	52.2 ± 9.5	6/12 (50)	24/114 (21)	26.6 ± 6.3
Diabetes mellitus	23/124 (18.5)	60.7 ± 8.9	3/11 (27)	20/113 (18)	31.0 ± 6.6
Sinus pilonidalis	21/123 (17.1)	50.4 ± 10.1	2/10 (20)	19/113 (17)	27.8 ± 7.6
Rheumatoid arthritis	16/124 (13.2)	57.4 ± 8.5	1/11 (9)	15/110 (14)	30.1 ± 7.5
Thyroid disease	16/127 (12.6)	52.6 ± 7.9	1/13 (8)	15/114 (13)	27.4 ± 6.1
Asthma/COLD	15/126 (11.9)	57.4 ± 7.2	2/13 (15)	13/113 (12)	26.7 ± 7.1
Acne back scarring	14/123 (11.4)	50.9 ± 10.9	4/12 (33)	10/111 (9)	27.9 ± 7.5
Inflammatory bowel disease	6/121 (5.0)	53.0 ± 9.2	0/9 (0)	6/112 (5)	26.5 ± 6.4
Stroke	3/126 (2.4)	46.7 ± 3.5	1/13(8)	2/113 (2)	23.3 ± 6.6

COLD - chronic obstructive lung disease; n - number; SD - standard deviation; x - patients with the disease
[a] Some participants left fields blank resulting in the slight variation in n

Treatment

A majority (61.0%, 64/105) had used systemic antibiotics, and fewer (46.9%, 45/96) had been treated with topical antibiotics. A majority (77.2%, 95/123) also indicated that they had been treated with incision, whereas treatment with excision or deroofing had been used in 55.8% (63/113) or 57.7% (64/111), respectively.

Prognostic factors

Looking at the association between smoking and development of disease, 48.5% (33/68) of former smokers or nonsmokers were disease-free, whereas only 28.8% (17/59) of the active smokers achieved remission (Figure 1). Approximately two-thirds (66.0%, 33/50) who reported remission of the disease were nonsmokers, whereas 34.0% were active smokers (17/50). The odds ratio (OR) for self-reported remission in nonsmoking participants was 2.8 (95% CI 1.3-6.3; $P = 0.012$). The association between obesity and evolution of disease is illustrated in Figure 2. Nonobese participants had an OR for remission of 3.9 (95% CI 1.4-11.0). HS remission was reported by 48.1% (26/54) of those not describing familial disposition, whereas 32.7% (16/49) of patients with a known first-degree relative with HS indicated remission of the disease (Figure 3). For participants with no known familial disposition, the OR for remission was nonsignificant (OR 0.6, 95% CI 0.3-1.4). When controlling for age, smoking and obesity the OR was 0.95 (95% CI 0.91-1.00; $P = 0.03$). However, the OR is only slightly smaller than 1. Sex was not associated with remission (OR 3.7, 95% CI 0.9-14.3; $P = 0.62$).

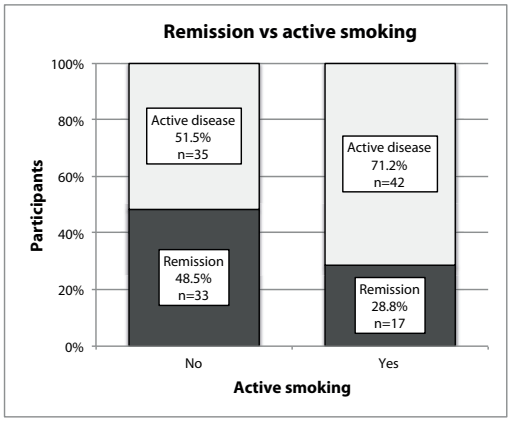


Figure 1. Association between active smoking and active hidradenitis suppurativa.

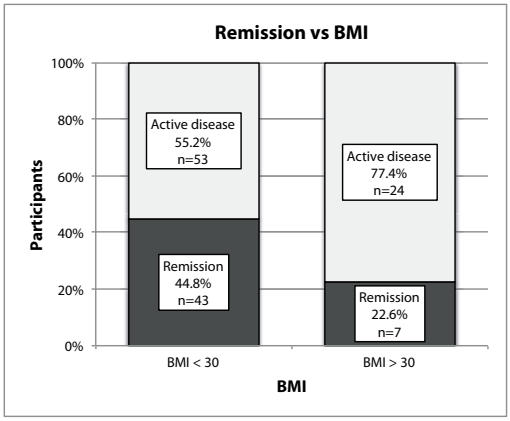


Figure 2. Association between body mass index (BMI) > 30 and active hidradenitis suppurativa.

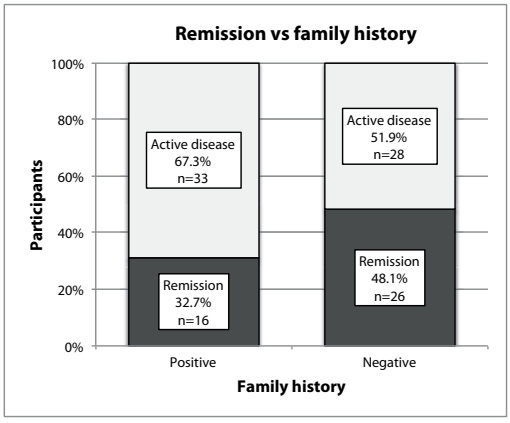


Figure 3. Association between family history of hidradenitis suppurativa and active disease.

DISCUSSION

The long-term evolution or prognosis of any disease is of interest not only to patients, but also to the treating physicians, yet for most diseases data beyond a 5-year horizon are scarce. We have therefore reported results regarding the course of HS after a mean follow-up of 22 years. We found that 39.4% of the sample reported remission of HS during this period. Previously suspected risk factors appeared to influence the chance of remission, as a majority of patients reporting remission also indicated that they had stopped smoking or had never smoked. We have previously shown that a 15% weight reduction in patients with BMI > 30 ameliorates HS.[16] Similarly, nonobesity was significantly linked to a higher rate of self-reported remission. Thus, the notion that lifestyle factors (i.e. nonsmoking and nonobesity) play a role in the development of many cases of HS appears to be supported by this survey. However, heredity may also play a role, as a familial disposition appeared to reduce the likelihood of remission, indicating that genetics may also be an important etiological factor.

The role of tobacco smoking with regard to HS is subject of much speculations. König *et al.* suggested smoking as the triggering factor, but indicated no specific mechanism.[13] In agreement with previous reports, in this study we found that > 90% of those who responded to our survey were active or former smokers. In earlier studies smoking has been reported at rates of 70-90% in populations of patients with HS.[13,18,21] Yet data on the possible beneficial effects of smoking cessation are rare. One study of *de novo* occurrence rates following surgery reported fewer or no new lesions following HS surgery when combined with smoking cessation.[21]

Kurzen *et al.* presented a host of potential mechanisms of cigarette smoking in the pathogenesis of HS.[2] These include the selectively inhibitory effect of alkaloids on microorganisms, with the exception of *Staphylococcus aureus*. Alkaloids appear to be able to trigger positive feedback promoting growth and proliferation of *S. aureus*, thus changing the microbiome. This possible mechanism is contradicted by the low prevalence of *S. aureus* found in HS lesions, although the preclinical evolution before symptoms occur may play a role. The prolonged secretion of nicotine in sweat is also mentioned as a possible cause. The effects of nicotine include epidermal hyperplasia, release of tumor necrosis factor alpha promotion of follicular occlusion and reduced macrophage and lymphocyte activity.[2] Tobacco smoke also contains polyaromatic carbohydrates, which may play a role in the development of HS.[22]

Our findings therefore lend support to the importance of tobacco in the etiology of HS. Surveys of disease severity have previously indicated a positive correlation between disease severity and smoking.[10] The present survey indicates that the chance of remission may be greater in those who stop smoking. This effect was most conspicuous for patients of normal weight, but a similar trend was noticed even in overweight patients.

Obesity is another possible risk factor. The supporting data consists of surveys of patients from many populations, as well as a positive correlation between BMI and disease severity.[10] In contrast to tobacco smoking, some evidence of a more dynamic association between BMI and HS has been published.[16] Data therefore exist to suggest that obesity is linked to the likelihood of developing HS and the severity of HS, and that weight reduction may improve HS.[16] The proposed underlying mechanisms include local factors on the surface of the skin due to the warm and humid milieu in the skin folds of obese patients, as well as shear forces from clothes and skin-skin contact.[15,16] More general factors such as the association between obesity and chronic low-grade inflammation may also be involved.[22]

Although statistically not significant, the genetic predisposition of patients may influence the prognosis of HS. Familial disposition to HS is commonly accepted, with approximately one-third of patients listing a positive family history of HS. Furthermore, some researchers have described an autosomal dominant inheritance pattern with a variable penetrance.[23,24] The molecular genetics of HS have been a topic of interest since the seminal identification of candidate genes by Wang *et al.* in 2010.[25] The authors reported mutations of genes regulating the transmembrane protein, γ-secretase. In some families loss-of-function mutations in γ-secretase seem to predispose for HS-like lesions.[25] Miskinyte *et al.* also reported associated mutations in the γ-secretase stabilizing protein nicastrin.[26] In contrast, Pink *et al.* were only able to find these mutations in a minority of the patients studied.[27]

This survey indicates a trend towards a lower chance of remission in those patients who report HS in a first- or second-degree relative compared with patients with no family history. This may imply the importance of genetic factors in a subgroup of patients. Confounders such as smoking or obesity did not explain the findings, and patients indicating no family history of HS appeared to be more overweight and smoke more, supporting the suggestion that different subpopulations of HS may exist.[28]

The validity of these observations obviously requires discussion. A postal questionnaire does not have the same reliability as a physical examination, yet it is suggested that the validity of self-reported disease evolution in a long-standing disease with such clear symptoms as HS may provide useful results. It is further hypothesized that the stringent inclusion criteria may have improved the validity of the observations. The initial diagnosis of HS was based on a physical examination by a dermatologist, and most of the patients had a disease sufficiently severe to warrant not only specialist referral, but also outpatient management at a hospital over a period of time, indicating a high likelihood that they were well acquainted with their disease.

The validity of results in this study is further supported by good response rates after a long follow-up period.[29] The fact that the patients in this study were similar, although recruited from two different countries, also supports the soundness of the observations,

as does the patient characteristics, which appear similar to those previously reported by von der Werth and Williams.[9] The follow-up period in this study is longer and the age span among participants is wider, indicating that the results are more likely to be representative with regard to the full course of the disease. The results are also in agreement with some of the proposed associations reported in recent literature indicating a possible link to the pathogenesis of the disease.

The response rate in our study is comparable with that in similar studies.[18,29,30] Response bias must nevertheless be considered, as it is generally accepted that persons with a particular symptom or condition are more likely to participate in studies related to that symptom or condition because of the relevance of the study to their lives.[29] Accordingly, the response rate to a HS-oriented questionnaire is likely to be higher in a group that feels affected by HS symptoms, thus potentially overestimating the prevalence of active disease and underestimating the rate of remission in this sample.

The sample shows large heterogeneity regarding age and follow-up period. It does not describe the entire lifespan or even duration of disease for every patient. We therefore cannot know whether patients with full remission will experience recurrences in the future or whether the patients who had only 12 years follow-up will achieve remission. Also, as we rely on self-reported outcomes for follow-up, uncertainties or imprecisions are likely. We have therefore interpreted the data conservatively.

REFERENCES

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

2 Kurzen H, Kurokawa I, Jemec GBE, *et al.* What causes hidradenitis suppurativa? *Exp Dermatol* 2008; **17**: 455–456.

3 Kimball AB, Kerdel F, Adams D, *et al.* Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med* 2012; **157**: 846–855.

4 Iorio ML, Ter Louw RP, Kauffman CL, Davison SP. Evidence-based medicine: facial skin malignancy. *Plast Reconstr Surg* 2013; **132**: 1631–1643.

5 Dahl M V. Granuloma annulare: long-term follow-up. *Arch Dermatol* 2007; **143**: 945–955.

6 Tosti A, Bellavista S, Iorizzo M. Alopecia areata: a long term follow-up study of 191 patients. *J Am Acad Dermatol* 2006; **55**: 438–441.

7 Gelmetti C, Rigoni C, Alessi E, *et al.* Pityriasis lichenoides in children: a long-term follow-up of eighty-nine cases. *J Am Acad Dermatol* 1990; **23**: 473–478.

8 Piraccini BM, Tosti A, Iorizzo M, Misciali C. Pustular psoriasis of the nails: Treatment and long-term follow-up of 46 patients. *Br J Dermatol* 2001; **144**: 1000–1005.

9 Von der Werth JM, Williams HC. The natural history of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2000; **14**: 389–392.

10 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

11 Sabat R, Chanwangpong A, Schneider-Burrus S, *et al.* Increased prevalence of metabolic syndrome in patients with acne inversa. *PLoS One* 2012; **7**: e31810.

12 Vazquez BG, Alikhan A, Weaver AL, *et al.* Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol* 2013; **133**: 97–103.

13 König A, Lehmann C, Rompel R, Happle R. Cigarette smoking as a triggering factor of hidradenitis suppurativa. *Dermatology* 1999; **198**: 261–264.

14 Cesko E, Körber A, Dissemond J. Smoking and obesity are associated factors in acne inversa: results of a retrospective investigation in 100 patients. *Eur J Dermatol* 2009; **19**: 490–493.

15 Deckers IE, van der Zee HH, Prens EP. Epidemiology of Hidradenitis Suppurativa: Prevalence, Pathogenesis, and Factors Associated with the Development of HS. *Curr Dermatol Rep* 2014; **3**: 54–60.

16 Kromann C, Ibler KS, Kristiansen V, Jemec GB. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol* 2014; **94**: 553–557.

17 Thomas CL, Gordon KD, Mortimer PS. Rapid resolution of hidradenitis suppurativa after bariatric surgical intervention. *Clin Exp Dermatol* 2014; **39**: 315–318.

18 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

19 Esmann S, Dufour DN, Jemec GBE. Questionnaire-based diagnosis of hidradenitis suppurativa: specificity, sensitivity and positive predictive value of specific diagnostic questions. *Br J Dermatol* 2010; **163**: 102–106.

20 Hojat M, Xu G. A visitor's guide to effect sizes–statistical significance versus practical (clinical) importance of research findings. *Adv Heal Sci Educ Theory Pract* 2004; **9**: 241–249.

21 Kurzen H, Schönfelder-Funcke S, Hartschuh W. [Surgical treatment of acne inversa at the university of Heidelberg]. *Coloproctology* 2000; **22**: 76–80 (in German).

22 van der Zee HH, Laman JD, Boer J, Prens EP. Hidradenitis suppurativa: viewpoint on clinical phenotyping, pathogenesis and novel treatments. *Exp Dermatol* 2012; **21**: 735–739.

23 Von der Werth JM, Williams HC, Raeburn JA. The clinical genetics of hidradenitis suppurativa revisited. *Br J Dermatol* 2000; **142**: 947–953.

24 Fitzsimmons JS, Guilbert PR. A family study of hidradenitis suppurativa. *J Med Genet* 1985; **22**: 367–373.

25 Wang B, Yang W, Wen W, *et al.* γ-secretase gene mutations in familial acne inversa. *Science* 2010; **330**: 1065.

26 Miskinyte S, Nassif A, Merabtene F, *et al.* Nicastrin mutations in French families with hidradenitis suppurativa. *J Invest Dermatol* 2012; **132**: 1728–1730.

27 Pink AE, Simpson MA, Desai N, *et al.* Mutations in the γ-secretase genes NCSTN, PSENEN, and PSEN1 underlie rare forms of hidradenitis suppurativa (acne inversa). *J Invest Dermatol* 2012; **132**: 2459–2461.

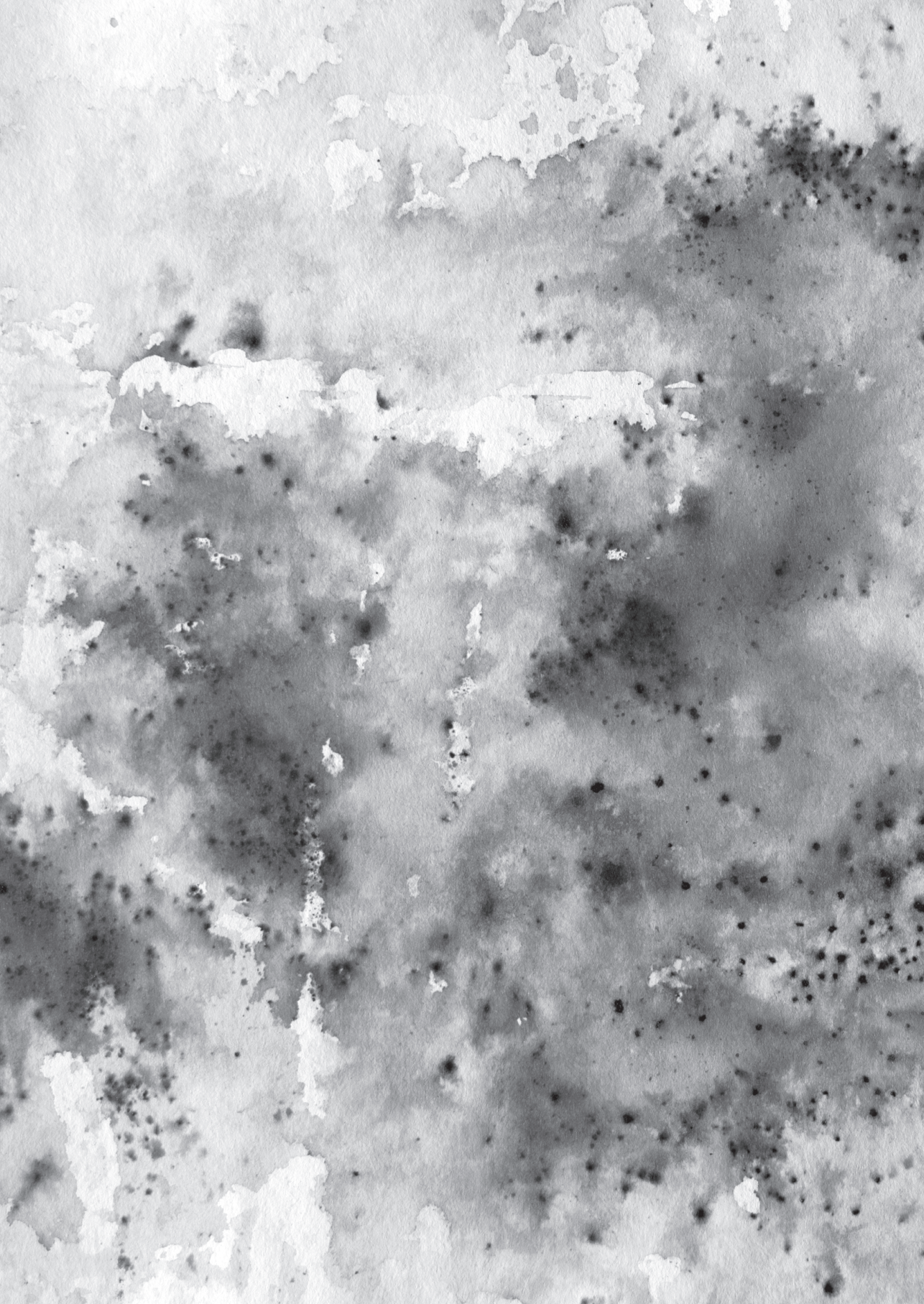
28 Canoui-Poitrine F, Le Thuaut A, Revuz JE, *et al.* Identification of three hidradenitis suppurativa phenotypes: Latent class analysis of a cross-sectional study. *J Invest Dermatol* 2013; **133**: 1506–1511.

29 Asch DA, Jedrziewski MK, Christakis NA. Response rates to mail surveys published in medical journals. *J Clin Epidemiol* 1997; **50**: 1129–1136.

30 Must A, Spadano J, Coakley EH, *et al.* The disease burden associated with overweight and obesity. *JAMA* 1999; **282**: 1523–1529.

Part II

Comorbidities of Hidradenitis Suppurativa



Chapter 5

Severe fatigue based on anemia in patients with hidradenitis suppurativa: report of two cases and a review of the literature

Inge E. Deckers, Hessel H. van der Zee, Errol P. Prens

J Eur Acad Dermatol Venereol. 2016;30:174-175

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease.[1] Patients often report fatigue, which is generally attributed to the debilitating psychosocial impact of HS.[2,3] However, sometimes severe anemia causes the fatigue. The co-occurrence of HS and anemia is mentioned in reviews on the disease,[1,4] but they refer to a single case series from 1968.[5] Since, no studies have been published on this subject. Therefore, we present two representative cases of severe HS with fatigue, based on chronic marked anemia.

The first case is a 46-year-old, otherwise healthy, man with a six-year history of HS, Hurley stage III, on his buttocks, groin and peri-genital area. He presented with purulent blood loss from his HS lesions and intense fatigue (Figure 1a). Previous treatments with isotretinoin and multiple antibiotics were ineffective. Laboratory tests revealed a microcytic anemia (hemoglobin (Hb): 4.5 mmol/L) (Table I), for which he received three packed-cells and was referred to internal medicine. Colonoscopy revealed no abnormalities, gastroscopy was discontinued because of patient's anxiety. Helicobacter Pylori-breathing test was negative. Iron supplementation was started, temporarily improving his hemoglobin level. Clindamycin 3dd200 mg yielded minor effect on his HS. Extensive wide excision was performed of all HS affected skin with closure by split-skin grafting. Six months postoperatively the wounds were healed (Figure 1b), his fatigue resolved and his hemoglobin level normalized (Hb: 9.4 mmol/L) (Table I).

The second case is a 61-year-old women, suffering from HS since the age of 14, Hurley stage III, located in the axillae, groin, pubic and gluteal area. She had a medical history of fatigue, diabetes and hypertension. Previous treatments with antibiotics were ineffective. Laboratory testing revealed normocytic anemia (Hb: 5.0 mmol/L) (Table I). She was referred to internal medicine who concluded that her anemia was caused by iron deficiency and chronic disease, since no other cause was found. She received multiple blood transfusions, temporarily increasing her hemoglobin. Adalimumab was started for her HS, with modest efficacy. Multiple extensive surgical excisions were performed on her axillae, groin and gluteal area, with subsequent blood loss requiring blood transfusions. Hereafter infliximab infusions were started. The remaining HS lesions improved and the hemoglobin level normalized (Hb 8.5 mmol/L) (Table I).

HS patients often report fatigue, which is attributed to the debilitating course and great psychological impact of HS.[2,3] However, a more general underlying cause, chronic marked anemia, is sometimes overlooked. In 1968, Tennant *et al.* reported on anemia associated with HS.[5] In their population, 10 out of 42 (24%) patients with severe HS had marked anemia (Hb < 6.3 mmol/L). They concluded that anemia was probably caused by chronic inflammatory processes.[5] Anemia as consequence of chronic disease is believed to be caused by the effects of elevated levels of pro-inflammatory cytokines.[6] Interferon-γ, interleukin (IL)- 1 and tumor necrosis factor alpha (TNF-α) can inhibit renal production of erythropoietin and reduce its physiological effect on the bone marrow.[6,7]

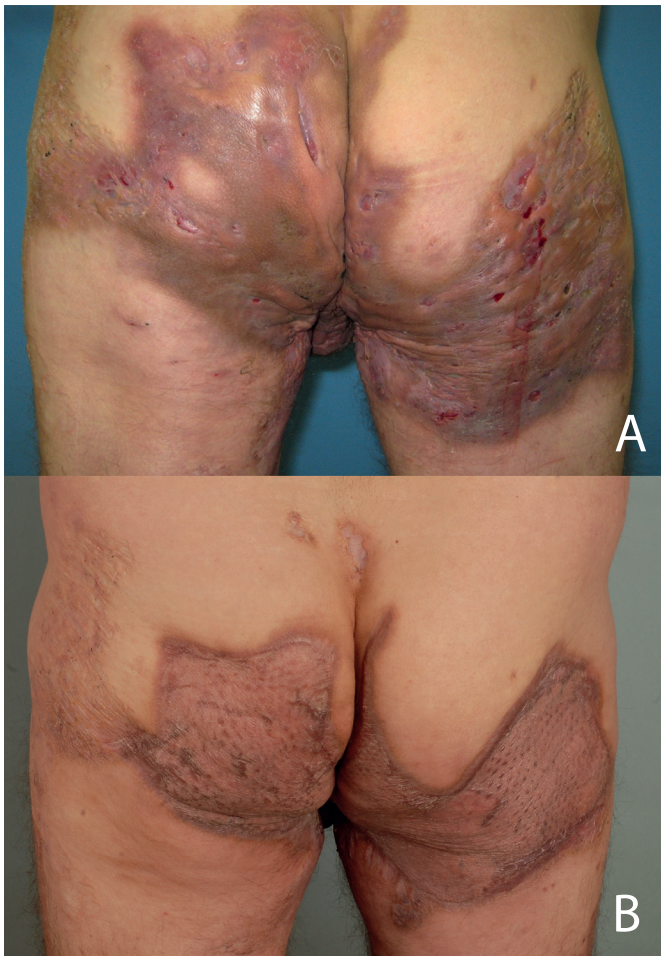


Figure 1. Hidradenitis suppurativa in a 46-year-old male. (a) At first presentation, note the sanguineous discharge from the fistulas. (b) Six months after extensive surgery.

Additionally, these cytokines can enhance the uptake of iron by activated macrophages,[6] whereas TNF-α can also decrease the intestinal iron absorption,[8,9] both resulting in less iron available for erythropoiesis. In HS, elevated levels of IL-1ß, IL-10 and TNF-α have been demonstrated.[10] We argue that these increased cytokine levels, contribute to the development of anemia in patients with severe HS. In addition, HS patients can lose significant amounts of blood via sanguineous drainage from their fistulas, also contributing to the development or preservation of anemia.

In conclusion, fatigue is often mentioned by HS patients and can be caused by severe anemia. It is important to check for anemia, especially when considering extensive surgery, and because the fatigue can worsen the already poor quality of life of HS patients.

Table I. Laboratory values of the first and second case

	Case 1: 46-year-old male		Case 2: 61-year-old female	
	First presentation	Six months after extensive surgery	First presentation	After six months of infliximab therapy
Hemoglobin (n: male: 8.6-10.5 mmol/l, female: 7.5-8.5 mmol/l)	4.5 mmol/l ↓	9.4 mmol/l	5.0 mmol/l ↓	8.5 mmol/l
Hematocrit (n: 0.40-0.50 l/l)	0.27 l/l ↓	0.45 l/l	0.27 l/l ↓	0.41 l/l
Erythrocytes (n: 4.40-5.60 *10^{12}/l)	3.95*10^{12}/l ↓	4.98*10^{12}/l	3.17*10^{12}/l ↓	-
MCV (n: 80-100 fL)	67 fL ↓	91 fL	84 fL	117 fL ↑
RDW (n: 12-16%)	19.2% ↑	16.9% ↑	18.9% ↑	14.5%
Thrombocytes (n: 150-370 *10^{9}/l)	937*10^{9}/l ↑	395*10^{9}/l ↑	590*10^{9}/l ↑	331*10^{9}/l
Leukocytes (n: 3.5-10.0 *10^{9}/l)	18.0*10^{9}/l ↑	15.8*10^{9}/l ↑	-	-
CRP (n: 0.0-9.0 mg/l)	86 mg/l ↑	-	226 mg/l ↑	48 mg/l ↑

CRP - C-reactive protein; MCV - mean corpuscular volume; n - normal value; RDW - red blood cell distribution width, ↑= enhanced level, ↓= decreased level

REFERENCES

1 Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. *J Am Acad Dermatol* 2009; **60**: 539–561.

2 Esmann S, Jemec GB. Psychosocial impact of hidradenitis suppurativa: a qualitative study. *Acta Derm Venereol* 2011; **91**: 328–332.

3 Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol* 2010; **90**: 264–268.

4 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

5 Tennant Jr F, Bergeron JR, Stone OJ, Mullins JF. Anemia Associated With Hidradenitis Suppurativae. *Arch Dermatol* 1968; **98**: 138–140.

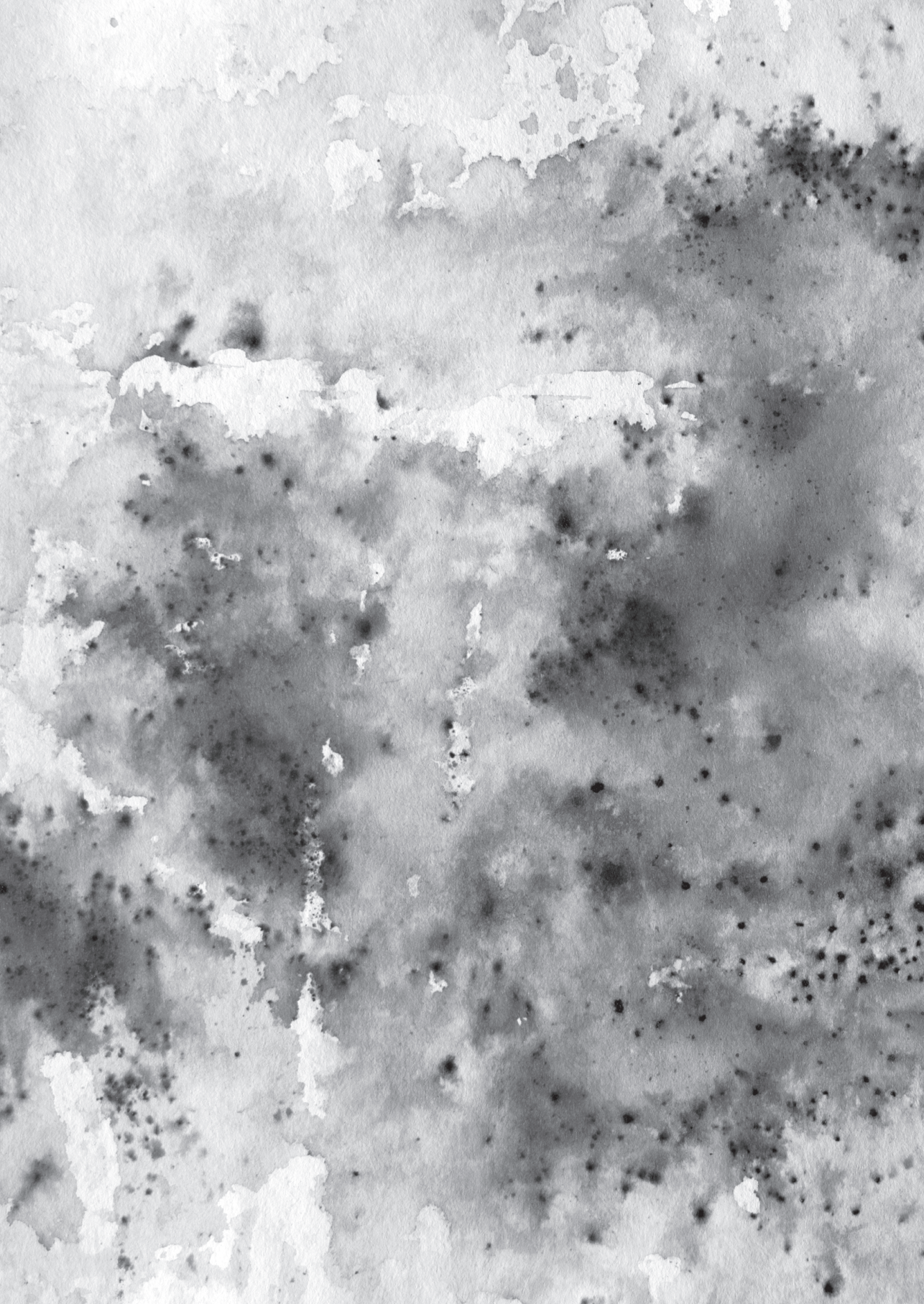
6 Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352**: 1011–1023.

7 Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. *J Interf cytokine Res* 1998; **18**: 555–559.

8 Johnson D, Bayele H, Johnston K, *et al.* Tumour necrosis factor alpha regulates iron transport and transporter expression in human intestinal epithelial cells. *FEBS Lett* 2004; **573**: 195–201.

9 Sharma N, Laftah AH, Brookes MJ, *et al.* A role for tumour necrosis factor alpha in human small bowel iron transport. *Biochem J* 2005; **390**: 437–446.

10 van der Zee HH, de Ruiter L, van den Broecke DG, *et al.* Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. *Br J Dermatol* 2011; **164**: 1292–1298.



Chapter 6

Inflammatory bowel disease is common in patients with hidradenitis suppurativa, but not a distinct phenotype; results from a multicenter cross-sectional study

Inge E. Deckers, Farida Benhadou, Marjolein Koldijk, Veronique del Marmol, Barbara Horváth, Jurr Boer, Hessel H. van der Zee, Errol P. Prens

Submitted for publication

ABSTRACT

Background: Hidradenitis suppurativa (HS) is a well-established comorbidity in inflammatory bowel disease (IBD; Crohn's disease or ulcerative colitis). However, the prevalence of IBD in patients with HS is unknown.

Objective: To determine the prevalence of IBD in patients with HS, and to determine if HS with associated IBD is a distinct HS phenotype.

Methods: For this multicenter cross-sectional study HS patients were actively asked if they had IBD during consultation, medical files were checked to confirm the diagnosis of IBD. In addition, clinical characteristics of all patients with HS were collected.

Results: IBD has prevalence of 3.3% (95% CI 2.3-4.4) in 1,076 HS patients. The prevalence of Crohn's disease was 2.5% (95% CI 1.6-3.4) and of ulcerative colitis was 0.8% (95% CI 0.3-1.4). HS-IBD patients were less frequently obese (13.9% vs 31.2%, $P = 0.04$) than HS-only patients, but there were no differences in gender, family history of HS, disease severity, or smoking status.

Conclusion: The prevalence of IBD in patients with HS (3.3%) is four to eight times higher than in the general Northern European population. However, patients with HS and IBD do not represent a distinct HS phenotype.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent nodules and abscesses followed by sinus tract formation and scarring. The axillary, inguinal and gluteal area are the most frequently involved body areas.[1,2] In Europe the prevalence of HS is approximately 1%, with women being affected three times more frequently than men.[3] The pathogenesis of HS is still not fully understood; but it is thought that genetic predisposition and aberrant immunity play important roles, combined with external risk factors such as smoking and obesity.[1,3,4] There is no cure for HS; treatment often consists of long-term topical or oral antibiotics, and biologics.[5] When extensive sinus tract formation or fibrosis is present, surgery becomes unavoidable, whereby all affected tissue should be excised.[5]

HS has frequently been associated with inflammatory bowel disease (IBD), usually with Crohn's disease (CD) and to a lesser extent with ulcerative colitis (UC).[6–9] HS and CD share various similarities. They are both chronic inflammatory diseases of which the pathogenesis is not fully understood, but in which an aberrant immunity is believed to play an important role.[4,10,11] Also smoking is a risk factor for both diseases and it can aggravate disease severity.[2,3,10] The clinical course of HS as well as of CD is characterized by periods of exacerbation and remission, and they respond well to biologics such as tumor necrosis factor alpha (TNF-α) inhibitors.[8,11,12] Also the clinical presentation of the diseases show similarities. Since in both diseases perianal involvement with sterile abscesses and sinus tracts can be present, it is almost impossible to differentiate between cutaneous CD and concurrent HS.[8,9]

Previous studies showed an association between HS and IBD. Based on a questionnaire among IBD patients a prevalence of 23% was suggested.[13] A more recent study, in which the questionnaire based diagnoses were confirmed by telephone, established a lower prevalence of 6.8-10.6%.[14] Moreover, Yadav *et al.* found in their population-based cohort study that only eight out of 679 IBD patients suffered from HS, resulting in a prevalence of 1.2%.[7] However, all these studies investigated the prevalence of HS in patients with IBD; the reverse association, HS patients who also suffer from IBD, has not yet been reported.

The aim of this study was to determine the prevalence of IBD in patients with HS, by actively asking 1,076 HS patients if they have IBD during intake, and by reviewing the gastroenterological medical files of those who answered affirmative. In addition, we assessed clinical features (e.g. disease characteristics, comorbidities and risk factors) in patients who had only HS, and those who had both IBD and HS, to determine whether these patients represented a distinct HS phenotype.

PATIENTS AND METHODS

For this multicenter cross-sectional study, data were collected between 2007 and 2015 from HS patients who visited the Departments of Dermatology at Erasmus Medical Center Rotterdam, The Netherlands (ID, HZ, EP); Deventer Hospital, The Netherlands (JB); University Medical Center Groningen, The Netherlands (MK, BH); and Hôpital Erasme, Belgium (FB, VM). The diagnosis HS was made based on the patients history of HS symptoms and physical examination.[1] For this type of analysis, medical ethical committee approval is not required under Dutch law.

Data collection

During consultations all consecutive HS patients were actively asked if they suffered from CD or UC. The affirmative responses were confirmed as IBD if the diagnosis IBD was made by a gastroenterologist based on endoscopy, preferably with histopathological evidence (further referred to as HS-IBD).

Clinical characteristics were further collected from the medical files, e.g. disease severity, age of onset of HS, family history of HS, and the body sites affected by HS. The Hurley classification was used to assess disease severity.[1] The body sites counted were: axillary, inguinal/femoral, gluteal, perianal and genital region. Abdomen, (infra)mammary and atypical regions were grouped as other. HS was considered familial, when a first- or second-degree relative also suffered from HS. Furthermore, patients' smoking habits were assessed, and BMI was calculated based on reported body weight and height.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (IBM Corp, Armonk, NY). The prevalence was calculated as the percentage with the 95% confidence interval (CI). Independent *t*-test was performed for normally distributed nominal data, presented as mean ± standard deviation (SD). Mann-Whitney U test for non-normally distributed nominal data, presented as median with the interquartile range [IQR]. A Pearson chi-square test ($n \geq 5$) or a Fisher exact test ($n < 5$) was used for categorical data, presented as number (n) with the corresponding percentage. Missing data were excluded from analysis. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Data were collected of 1,076 HS patients, 324 males (30.1%) and 752 females (69.9%), with a mean age of 38.4 ± 12.7 years. Most patients had Hurley stage I (43.9%) or stage II (44.2%) and suffered from HS for a median period of 11.0 years [IQR: 5.0-21.0] (Table I).

Table I. General characteristics and comparison of patients with solely hidradenitis suppurativa versus patients with both hidradenitis suppurativa and inflammatory bowel disease (HS-IBD)

	All patients (n=1076)	**HS** (n=1040)	**HS-IBD** (n=36)	***P*-value**[a]
Gender, n (%)				
- Female	752 (69.9)	725 (69.7)	27 (75.0)	0.58
- Male	324 (30.1)	315 (30.3)	9 (25.0)	
Age years, mean ± SD	38.4 ± 12.7	38.5 ± 12.7	36.5 ± 12.6	0.37
Age of disease onset of HS years, mean ± SD	23.9 ± 10.7	23.9 ± 10.7	23.8 ± 10.0	0.97
Disease duration of HS years, median [IQR]	11.0 [5.0-21.0]	12.0 [5.0-21.0]	9.0 [3.0-16.0]	0.14
Family history of HS, n (%)				
- Positive	353 (35.8)	343 (36.0)	10 (30.3)	0.58
Smoking status, n (%)				
- Current smoker	700 (65.7)	680 (66.1)	20 (55.5)	0.37
- Ex-smoker	137 (12.9)	132 (12.8)	5 (13.9)	
- Nonsmoker	228 (21.4)	217 (21.1)	11 (30.6)	
BMI kg/m^2, mean ± SD	27.8 ± 6.0	27.9 ± 6.0	25.4 ± 5.1	**0.01**
BMI subgroups,[b] n (%)				
- Normal weight	389 (37.3)	369 (36.6)	20 (55.6)	**0.04**
- Overweight	336 (32.2)	325 (32.2)	11 (30.5)	
- Obese	319 (30.5)	314 (31.2)	5 (13.9)	
Hurley stage, n (%)				
- Stage I	472 (43.9)	460 (44.2)	12 (33.3)	0.27
- Stage II	476 (44.2)	455 (43.8)	21 (58.3)	
- Stage III	128 (11.9)	125 (12.0)	3 (8.4)	
Affected body regions, n (%)				
- Axillary	679 (63.3)	658 (63.5)	21 (58.3)	0.60
- Inguinal/femoral	899 (83.8)	871 (84.0)	28 (77.8)	0.36
- Genital	337 (31.4)	321 (31.0)	16 (44.4)	0.10
- Gluteal	460 (42.9)	444 (42.8)	16 (44.4)	0.87
- Perianal	218 (20.3)	208 (20.0)	10 (27.8)	0.29
- Other[c]	373 (34.8)	366 (35.3)	7 (19.4)	0.05

BMI - body mass index; HS - hidradenitis suppurativa; HS-IBD - hidradenitis suppurativa patients with inflammatory bowel disease

[a] *P*-value of independed *t*-test or Mann Whitney U test for continuous data and two-side chi-square test or Fisher exact test for categorical data

[b] Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

[c] Other: mammary region, abdominal region or atypical regions affected

IBD has a prevalence of 3.3% in patients with HS

In 36 out of 1,076 HS patients the diagnosis IBD could be confirmed, resulting in a prevalence of 3.3% (95% CI 2.3-4.4). Of these 36 HS-IBD patients, 27 suffered from CD (75.0%) and nine from UC (25.0%), resulting in a prevalence of 2.5% (95% CI 1.6-3.4) for CD and 0.8% (95% CI 0.3-1.4) for UC in patients with HS.

Clinical characteristics of HS-IBD patients

The clinical characteristics of the 36 HS-IBD patients are shown in Table II and in Supplement Table I. HS-IBD patients developed symptoms of HS at a mean age of 23.8 ± 10.0 years, whereas their IBD symptoms started at a mean age of 26.9 ± 11.2 years. From 31 of the 36 HS-IBD patients the age of onset of both diseases was known. Fifteen of these patients had HS before developing IBD (48.4%), four developed HS and IBD at the same

Table II. Clinical characteristics of patients with hidradenitis suppurativa and inflammatory bowel disease

	HS and Crohn's disease (n=27)	**HS and ulcerative colitis** (n=9)
Gender, n (%)		
- Female	20 (74.1)	7 (77.8)
- Male	7 (25.9)	2 (22.2)
Age of disease onset of HS years, median [IQR]	23.0 [16.0-28.0]	19.5 [16.0-24.5]
Age of disease onset of IBD years, median [IQR]	23.0 [17.3-35.3]	29.0 [25.0-39.3]
First HS or first IBD, n (%) (n=31)		
- First developed HS	10 (41.7)	5 (71.4)
- First developed IBD	10 (41.7)	2 (28.6)
- HS and IBD at same time	4 (16.7)	0
Family history of HS, n (%)		
- Positive	7 (28.0)	3 (37.5)
Smoking status, n (%)		
- Current smoker	14 (51.9)	6 (66.7)
- Ex-smoker	4 (14.8)	1 (11.1)
- Nonsmoker	9 (33.3)	2 (22.2)
BMI kg/m^2, median [IQR]	23.0 [21.2-26.3]	27.1 [21.8-32.8]
BMI subgroups,[a] n (%)		
- Normal weight	16 (59.3)	4 (44.4)
- Overweight	9 (33.3)	2 (22.2)
- Obese	2 (7.4)	3 (33.3)
Hurley stage, n (%)		
- Stage I	9 (33.3)	3 (33.3)
- Stage II	15 (55.6)	6 (66.7)
- Stage III	3 (11.1)	0
Affected body regions, n (%)		
- Axillary	16 (59.3)	5 (55.6)
- Inguinal/femoral	20 (74.1)	8 (88.9)
- Genital	10 (37.0)	6 (66.6)
- Gluteal/perianal	13 (48.1)	5 (55.6)
- Other[b]	3 (11.1)	4 (44.4)

BMI - body mass index; HS - hidradenitis suppurativa; IBD - inflammatory bowel disease

[a] Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

[b] Other: mammary region, abdominal region or atypical regions affected

time (12.9%), and twelve patients had symptoms of IBD before developing HS (38.7%). Especially patients with UC had HS before they developed symptoms of UC (Table II).

HS-IBD is not a distinct HS phenotype

When comparing the clinical characteristics of the 36 HS-IBD patients with the 1,040 HS patients, we found that obesity was significantly less frequent among HS-IBD patients (13.9% vs 31.2%; $P = 0.04$). In addition, HS-IBD patients were more often affected in the genital area (44.4% vs 31.0%), whereas less frequently affected in the atypical body areas (19.4% vs 35.3%); however, these differences were not significant. There was no difference in gender, family history of HS, disease severity, disease duration or smoking status (Table I).

DISCUSSION

This multicenter cross-sectional study shows that 36 out of 1,076 HS patients (3.3%) had IBD, resulting in a prevalence of 2.5% for CD and 0.8% for UC in HS patients. In comparison, the estimated prevalence of IBD in the general population in Northern Europe ranges between 0.41% and 0.74%; with a prevalence of CD between 0.14% and 0.32% and of UC between 0.24% to 0.41%.[15–18] These data indicate that the prevalence of IBD is four to eight times higher in our HS cohort than in the general population. For CD, the prevalence is even eight to eighteen times higher. These results confirm the previously observed association between HS and IBD, especially between HS and CD.[6,8,14,19]

When comparing clinical characteristics of HS-IBD patients with HS-only patients, we found that only 14% of the HS-IBD patients were obese compared with a third of the HS-only patients. This might be explained by the finding that IBD patients more often suffer from malnutrition and weight loss.[20] We anticipated to find more perianal involvement of HS and a higher percentage of smokers among HS-IBD patients.[12,21] However, this could not be confirmed by our data. HS-IBD patients, especially patients with UC, were more often affected in the genital area, but this was not significant. Therefore, our data indicate that HS-IBD patients do not present a distinct HS phenotype, since there was no difference in gender, disease severity, family history of HS or smoking status between HS-IBD and HS-only patients.[7,13]

It has been reported that IBD usually precedes HS;[13,19,21] however, in our population more patients developed HS before IBD. Because IBD can develop later, dermatologist should pay attention to symptoms of IBD. When HS patients present with IBD suspicious symptoms, e.g. bloody stool or recurrent abdominal pain, they should be referred to a gastroenterologist for further analysis.

The association of HS and IBD is conceivable as they share multiple similarities. First, smoking triggers both HS and CD, and smokers tend to have more severe disease than nonsmokers.[10,22] However, in UC patients, smoking tends to have protective effect.[10] Since most HS patients were active or former smokers, this might explain the lower prevalence of UC in HS patients. Second, HS and cutaneous CD share clinical and histological similarities making it difficult to differentiate in certain cases.[23,24] Both can present with perianal inflammatory lesions, abscesses and sinus tract formation. Histology cannot differentiate HS from CD since both diseases are characterized by the presence of diffuse tissue inflammation with epithelioid granulomas.[23,24] Cutaneous CD is most likely when enterocutaneous fistulas are present and/or no other skin regions are affected by typical HS lesions. Concurrent HS is more likely when other body areas are also affected by HS.[6,9,11] An endoscopy or radiological imaging is advisable when perianal sinuses or fistulas are present in patients with HS. Third, the clinical improvement induced by anti-TNF-α in both diseases also suggests a shared inflammatory pathway.[11,12] Interestingly in both diseases infliximab is an effective treatment, whereas they both show only minor response on etanercept.[5,25] Furthermore, involvement of the interleukin (IL)-23/Th-17 pathway is suggested in both CD and HS.[10,26] Finally, HS and IBD both have a genetic predisposition. In CD polymorphisms in DNA-regions containing nucleotide oligomerization domain 2 (NOD2) genes are implicated.[10,27] However, in two small pilot studies, polymorphisms in the CARD15/NOD2 coding sequence were not confirmed in HS.[27,28] In a larger IBD cohort higher frequencies of the single-nucleotide polymorphisms SULT1B1, SULT1E1 and ELOVL7 were found in patients with HS and IBD, which might be potential candidate genes for HS.[14] However, no causative genes have yet been identified for HS and more research is needed to determine which genetic alterations are associated with HS.[29]

Our study is the first to determine the prevalence of IBD in a large cohort of patients with HS, whereby each HS patient was seen and diagnosed by a dermatologist. However, our study also has limitations; the prevalence of IBD might be underestimated, because some HS patients could still develop IBD in the future. A prospective registry in which patients are followed for multiple years would provide a better opportunity to determine the exact prevalence of IBD in HS. However, these registries are still in their infancy, therefore it will take years before results of such studies will be available.[30,31] Because there are no prevalence data available of IBD in the Netherlands and Belgium, we used IBD data from Germany, The United Kingdom, Denmark and Sweden to compare our prevalence. We are aware that in Europe the incidence of IBD is higher in Northern European countries than in Southern countries;[32] therefore we have chosen these countries, as they are geographically near to the Netherlands and Belgium.

Concluding, in this study we show a prevalence of 3.3% of IBD in patients with HS, which is four to eight times higher than in the general Northern European population.

Because it is not possible to identify IBD patients by their HS phenotype, it is advisable to ask patients with HS about abdominal complaints, such as recurrent abdominal pain and bloody stool. If IBD is suspected or patients have intersphincteric fistulas, an endoscopy is advisable to exclude IBD.

REFERENCES

1 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

2 Schrader AMR, Deckers IE, van der Zee HH, *et al.* Hidradenitis suppurativa: A retrospective study of 846 Dutch patients to identify factors associated with disease severity. *J Am Acad Dermatol* 2014; **71**: 460–467.

3 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

4 Deckers IE, van der Zee HH, Prens EP. Epidemiology of Hidradenitis Suppurativa: Prevalence, Pathogenesis, and Factors Associated with the Development of HS. *Curr Dermatol Rep* 2014; **3**: 54–60.

5 Zouboulis CC, Desai N, Emtestam L, *et al.* European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; **29**: 619–644.

6 Kamal N, Cohen BL, Buche S, *et al.* Features of patients with Crohn's disease and hidradenitis suppurativa. *Clin Gastroenterol Hepatol* 2016; **14**: 71–79.

7 Yadav S, Singh S, Varayil JE, *et al.* Hidradenitis suppurativa in patients with inflammatory bowel disease: a population-based cohort study in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2016; **14**: 65–70.

8 Van der Zee HH, Van Der Woude CJ, Florencia EF, Prens EP. Hidradenitis suppurativa and inflammatory bowel disease: are they associated? Results of a pilot study. *Br J Dermatol* 2010; **162**: 195–197.

9 Yazdanyar S, Miller IM, Jemec GB. Hidradenitis suppurativa and Crohn's disease: Two cases that support an association. *Acta Dermatovenerol Alp Panon Adriat* 2010; **19**: 23–25.

10 Abraham C, Cho JH. Mechanisms of disease; Inflammatory Bowel Disease. *N Engl J Med* 2009; **361**: 2066–2078.

11 Roussomoustakaki M, Dimoulios P, Chatzicostas C, *et al.* Hidradenitis suppurativa associated with Crohn's disease and spondyloarthropathy: response to anti-TNF therapy. *J Gastroenterol* 2003; **38**: 1000–1014.

12 Blazquez I, Gonzalez-Lama Y, Roustan G. Crohn's disease and Hidradenitis suppurativa. An uncommon association that responds to Infliximab. *J Crohn's Colitis* 2013; **7**: e717–e718.

13 van der Zee HH, de Winter K, Van Der Woude CJ, Prens EP. The prevalence of hidradenitis suppurativa in 1093 patients with inflammatory bowel disease. *Br J Dermatol* 2014; **171**: 673–675.

14 Janse IC, Koldijk MJ, Spekhorst LM, *et al.* Identification of clinical and genetic parameters associated with hidradenitis suppurativa in inflammatory bowel disease. *Inflamm Bowel Dis* 2016; **22**: 106–113.

15 Hein R, Köster I, Bollschweiler E, Schubert I. Prevalence of inflammatory bowel disease: estimates for 2010 and trends in Germany from a large insurance-based regional cohort. *Scand J Gastroenterol* 2014; **49**: 1325–1335.

16 Büsch K, Ludvigsson JF, Ekström-Smedby K, *et al.* Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. *Aliment Pharmacol Ther* 2014; **39**: 57–68.

17 Rubin GP, Hungin APS, Kelly PJ, Ling J. Inflammatory bowel disease: epidemiology and management in an English general practice population. *Aliment Pharmacol Ther* 2000; **14**: 1553–1559.

18 Jacobsen BA, Fallingborg J, Rasmussen HH, *et al.* Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978–2002. *Eur J Gastroenterol Hepatol* 2006; **18**: 601–606.

19 Eppinga H, Thio HB, van der Woude CJ. Characteristics of patients with Hidradenitis Suppurativa and Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2015; **Epub ahead of print**.

20 Bryant R V, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38**: 213–225.

21 Church JM, Fazio VW, Lavery IC, *et al.* The differential diagnosis and comorbidity of hidradenitis suppurativa and perianal Crohn's disease. *Int J Colorectal Dis* 1993; **8**: 117–119.

22 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

23 Attanoos RL, Appleton MAC, Hughes LE, *et al.* Granulomatous hidradenitis suppurativa and cutaneous Crohn's disease. *Histopathology* 1993; **23**: 111–115.

24 Roy MK, Appleton MAC, Delicata RJ, *et al.* Probable association between hidradenitis suppurativa and Crohn's disease: significance of epithelioid granuloma. *Br J Surg* 1997; **84**: 375–376.

25 Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *N Engl J Med* 2013; **369**: 754–762.

26 Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011; **65**: 790–798.

27 Nassar D, Hugot JP, Wolkenstein P, Revuz J. Lack of association between CARD15 gene polymorphisms and hidradenitis suppurativa: a pilot study. *Dermatology* 2007; **215**: 359.

28 van Rappard DC, Mekkes JR. Hidradenitis suppurativa not associated with CARD15/NOD2 mutation: a case series. *Int J Dermatol* 2014; **53**: e77–e79.

29 Ingram JR, Abbott R, Ghazavi M, *et al.* The Hidradenitis Suppurativa Priority Setting Partnership. *Br J Dermatol* 2014; **171**: 1422–1427.

30 Ingvarsson G, Dufour DN, Killasli H, *et al.* Development of a clinical Scandinavian registry for hidradenitis suppurativa; HISREG. *Acta Derm Venereol* 2013; **93**: 350–351.

31 Daxhelet M, Suppa M, Benhadou F, *et al.* Establishment of a European Registry for hidradenitis suppurativa/acne inversa by using an open source software. *J Eur Acad Dermatol Venereol* 2015; **Epub ahead of print**.

32 Shivananda S, Lennard-Jones J, Logan R, *et al.* Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 1996; **39**: 690–697.

Supplement Table I. Clinical characteristics of the 36 patients with hidradenitis suppurativa and inflammatory bowel disease

Patient ID	Sex; Age (years)	Smoking status	IBD	Age onset HS (years)	Age onset IBD (years)	Hurley stage	Body regions affected[a]
1	M; 17	No	CD	16	11	I	axillary
2	M; 18	Yes	CD	16	12	I	axillary, inguinal, gluteal
3	F; 20	No	CD	11	-	II	axillary, inguinal, gluteal
4	F; 21	Yes	CD	19	17	I	inguinal
5	F; 23	No	CD	16	16	I	axillary
6	M; 25	No	CD	22	-	II	axillary
7	F; 26	No	UC	14	-	II	axillary, inguinal, genital, gluteal
8	M; 26	Yes	CD	16	-	III	axillary, inguinal, gluteal, perianal, other
9	F; 28	Yes	UC	16	10	II	axillary, inguinal, other
10	F; 28	Quit	CD	23	23	II	inguinal, genital
11	F; 28	No	CD	20	21	II	axillary, other
12	M; 29	Yes	UC	26	29	II	axillary, inguinal, genital, gluteal
13	F; 30	Yes	CD	28	11	I	inguinal
14	F; 31	No	CD	24	30	I	inguinal, gluteal
15	F; 32	Quit	CD	16	17	II	axillary, inguinal, gluteal, perianal
16	F; 32	Yes	CD	24	19	II	axillary, genital, gluteal, perianal
17	F; 33	Yes	UC	20	29	II	inguinal, genital
18	F; 34	Yes	UC	19	28	II	inguinal, genital, other
19	F; 34	Yes	CD	31	18	II	inguinal
20	F; 36	Yes	CD	20	18	II	axillary, inguinal, genital, perianal, other
21	F; 37	Yes	CD	36	27	II	axillary, inguinal, genital
22	F; 37	Quit	CD	26	20	I	axillary, inguinal
23	F; 38	No	CD	23	23	III	genital
24	F; 41	Yes	CD	23	23	II	inguinal
25	F; 41	Yes	UC	16	24	I	axillary, inguinal, gluteal, perianal, other
26	F; 41	No	CD	10	30	II	inguinal, genital, gluteal, perianal
27	F; 45	Yes	CD	26	29	II	axillary, inguinal, perianal
28	M; 46	Quit	CD	40	43	II	axillary, inguinal, gluteal, perianal
29	F; 48	Quit	UC	20	34	I	inguinal, genital
30	F; 48	Yes	UC	47	41	I	axillary, inguinal, genital, gluteal, other
31	F; 50	Yes	CD	22	47	I	inguinal, genital
32	F; 50	No	CD	32	42	I	axillary, inguinal, genital, gluteal

Supplement Table I. Clinical characteristics of the 36 patients with hidradenitis suppurativa and inflammatory bowel disease (continued)

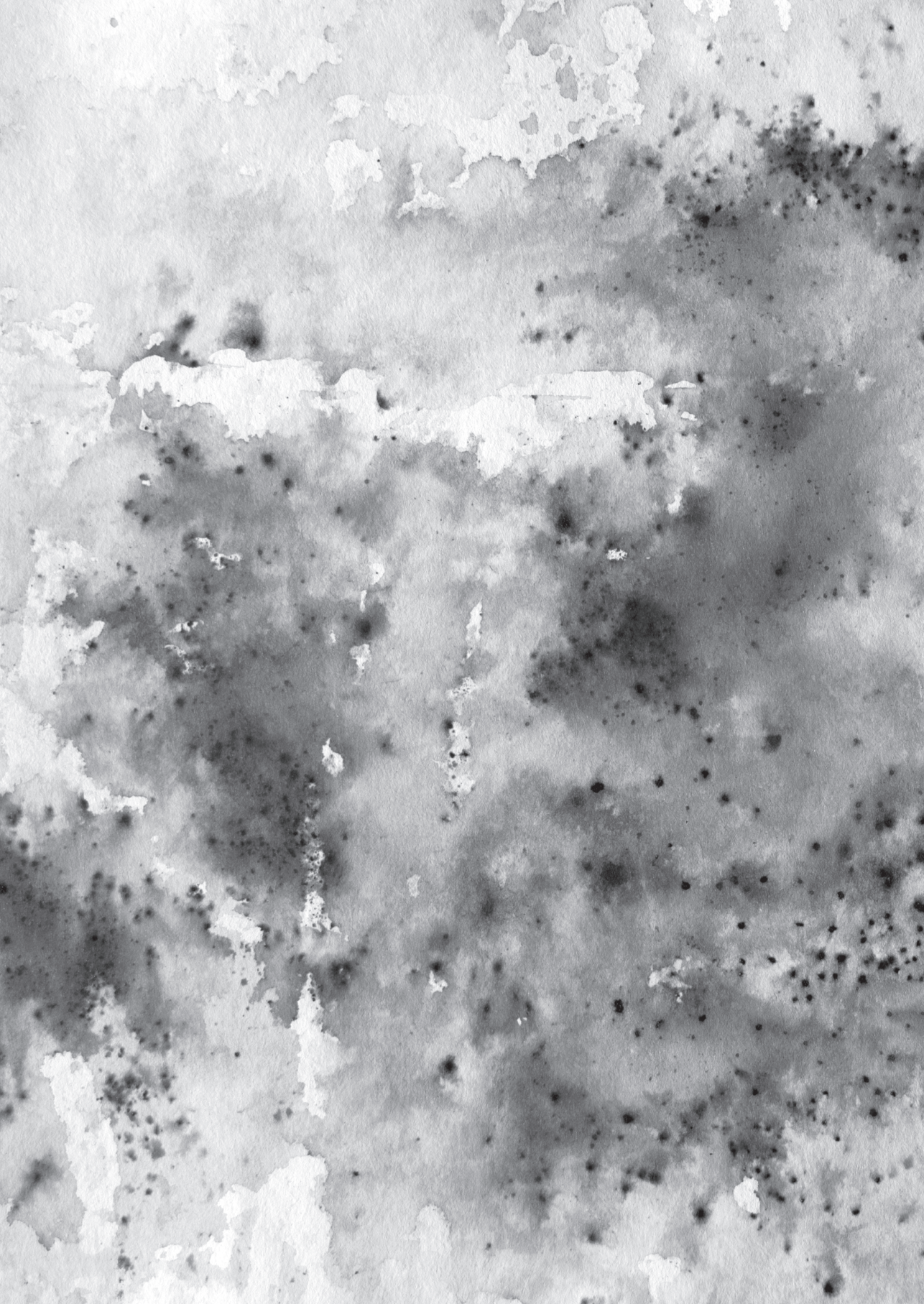
Patient ID	Sex; Age (years)	Smoking status	IBD	Age onset HS (years)	Age onset IBD (years)	Hurley stage	Body regions affected[a]
33	M; 53	Yes	CD	42	43	II	inguinal, gluteal, perianal
34	F; 56	Yes	CD	19	37	II	axillary, inguinal, genital
35	M; 63	Yes	CD	55	47	III	genital, gluteal, perianal
36	M; 70	No	UC	-	43	II	gluteal

IBD - inflammatory bowel disease; HS - hidradenitis suppurativa; M - male; F - female; CD - Crohn's disease; UC - ulcerative colitis. Missing data are marked with -

[a] Other; mammary region, abdominal region or atypical regions affected

Part III

The Impact of Hidradenitis Suppurativa



Chapter 7

Sexual health and quality of life are severely impaired in hidradenitis suppurativa: a multicenter cross-sectional study

Ineke C. Janse, Inge E. Deckers, Anita D. van der Maten, Andrea W.M. Evers, Jurr Boer, Hessel H. van der Zee, Errol P. Prens, Barbara Horváth

Submitted for publication

ABSTRACT

Background: Hidradenitis suppurativa (HS) has a major impact on the quality of life (QoL). Although it has commonly been assumed that HS impairs sexual health, only a single case-control study has been performed on sexual functioning in a small group of HS patients.

Objectives: The objective of this study was to investigate the QoL with a particular focus on sexual health in a substantial population of HS patients.

Methods: In total, 916 HS patients received an invitation to participate in this multi-center cross-sectional survey.

Results: 300 patients completed the questionnaires. This study showed a diminished QoL and sexual health in HS patients (FSFI score: 21.6 ± 9.6, IIEF score: 49.7 ± 20.7, ASEX score: 16.7 ± 5.3 and DLQI score: 12.5 ± 7.5). Sexual health was associated with QoL in women but not in men. Female gender and late onset of HS were associated with poor sexual function. Impairment of QoL was associated with anogenital involvement, early onset of HS, disease severity and disease activity.

Limitations: The sexual health questionnaires were not validated for patients with chronic skin diseases.

Conclusion: HS is associated with an impaired sexual health and QoL. Physicians should not hesitate to ask HS patients about their sexual function and, when needed, offer them psychological support.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease of the folliculopilosebaceous unit with a European prevalence of approximately 1% and a female preponderance of 3:1.[1] HS is characterized by the presence of painful nodules, draining sinuses and bridged scars at inverse body sites.[2,3] The incidence is the highest between the second and third decade of life.[4,5]

Previous studies have demonstrated that HS has a great impact on quality of life (QoL).[6–11] Compared with patients who suffer from other chronic skin diseases like psoriasis or neurofibromatosis type 1, HS patients have the lowest QoL.[6–11] Impairment in QoL in HS seems to be associated with disease severity.[6–10]

One of the key components of QoL is sexual functioning, which involves physical, psychological and emotional factors.[12] Sexual dysfunction refers to a disturbance in one of the following phases of the sexual response cycle: sexual desire, sexual arousal, orgasm and resolution.[13,14] As HS usually affects intimate body regions and occurs during young adulthood, it is plausible that HS influences sexual health. Kurek *et al.*[15] found sexual dysfunctioning in all 44 HS patients. Sexual function was more impaired in women than in men.[15]

Although it has been assumed that HS impairs sexuality, the study of Kurek *et al.*[15] is the only case-control study that has been performed on sexual functioning in HS.[15] Because this study was carried out in a limited number of patients, the impact of HS on sexual health and QoL remains unclear. Therefore, the objective of this study was to investigate QoL with a particular focus on sexual health in a larger group of patients with HS. Additionally, we aimed to identify parameters associated with impaired sexual health and QoL in HS.

MATERIALS AND METHODS

Subjects and design

This multicenter cross-sectional study was performed in the Dermatology Departments of the University Medical Center Groningen (UMCG), Erasmus Medical Center Rotterdam and Deventer Hospital, The Netherlands. In total, 916 patients diagnosed with HS between 2007 and September 2014 received a postal invitation to participate in this study. The diagnosis was made by a dermatologist and it was based on patients history and on physical examinations.[3] Patients with HS that visited the website of the hidradenitis patients' association were also invited.[16] An online questionnaire was available from the fourth of May until the third of August 2015 via a link on the website of the hidradenitis patients' association (Qualtrics 2015, LLC, Provo, Utah). A reminder was sent to nonrespondents after five weeks. The UMCG Ethics Committee confirmed that this

study, because of its non-interventional character, did not need to undergo full medical ethical review.

Questionnaire

To gain valid insight in the impact of the disease, the timespan covered by the questionnaires was set at one year.

Patient characteristics and disease severity

The questionnaire collected information on patient characteristics as shown in Table I. Disease severity was determined by using the pain score on the visual analog scale (VAS), patient global assessment (PtGA) and Hurley score.[17] Our PtGA ranged from 'complete control of disease' (score of 0) to 'no control of disease' (score of 3); a PtGA score ≥ 1 was defined as active disease.

Sexual health questionnaires

Three self-administered questionnaires were used for the assessment of sexual health: the Female Sexual Function Index (FSFI),[18–20] International Index of Erectile Function (IIEF)[21,22] and Arizona Sexual Experience scale (ASEX).[23] Sexual dysfunction is indicated in females by a FSFI score ≤ 26.55; in males it is indicated if the erectile function domain score of the IIEF is ≤ 25.[18,19,22] A total ASEX score of ≥ 19, any one item with a score of ≥ 5 or any three items with a score of ≥ 4 indicates sexual dysfunction for both genders.[23] A high score on the FSFI and IIEF indicates a better sexual function whereas a high score on the ASEX indicate greater impairment in sexual health. To determine if patients have had sexual intercourse in the past year, we used IIEF question 3 and FSFI question 17.

Quality of life questionnaire

The Dermatology Life Quality Index (DLQI) is a commonly used questionnaire for the assessment of QoL in skin diseases, in which a higher score indicates greater impairment of the QoL.[24,25]

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). In case of missing values in the DLQI, the score was calculated according to the procedure described in the manual. For the FSFI and IIEF, missing item-scores were replaced by the mean score of the other items of the same domain. The ASEX score was not calculated if scores were missing.

Descriptive statistics were applied to report the questionnaire outcomes. All continuous outcomes were described as mean ± standard deviation (SD). To calculate the differences between mean scores of two groups in normally distributed data, the

independent Student's *t*-test was used. The Pearson correlation coefficient (r) and the Spearman correlation coefficient (r_s) were used to determine correlations. A *P*-value less than 0.05 was considered statistically significant.

Table I. Patient characteristics

	n=300
Gender, n (%)	
- Male	66 (22)
- Female	234 (78)
Age years, mean ± SD	44.6 ± 12.3
Anogenital involvement, n (%)	
- Yes	117 (39)
- No	183 (61)
Relationship status, n (%)	
- In a relationship	226 (75)
- Not in a relationship	74 (25)
BMI kg/m^2, mean ± SD	28.1 ± 6.2
Current smoking behavior, n (%)	
- Smoker	171 (57)
- Nonsmoker	129 (43)
Age of onset years, mean ± SD	24.3 ± 11.6
Duration of disease years, mean ± SD	20.7 ± 11.2
VAS pain score, mean ± SD	4.7 ± 2.8
PtGA, n (%)	
- Reasonable control of disease	99 (33)
- Limited control of disease	132 (44)
- No control of disease	69 (23)
Hurley stage, n (%)	
- Stage I	96 (32)
- Stage II	123 (41)
- Stage III	81 (27)

BMI - body mass index; PtGA - patient global assessment; VAS - visual analog scale

RESULTS

Inclusion and exclusion

Of the 916 invited patients, seven patients refused participation, three patients were unable to participate because of comorbidity (Down's syndrome or mental illness) and 573 patients did not respond to the invitation. A total of 333 patients filled out the questionnaire, which corresponds with a response rate of 36%. Additionally to the 333 patients, 22 patients were included through application via the Dutch hidradenitis patients' association website. The questionnaires of 31 patients were returned incompletely

and therefore excluded. A PtGA score of 0 was found in 24 patients; these patients were only included in the analyses regarding disease activity. The final sample for analysis consisted of 300 HS patients.

Subjects

In total 66 men and 234 women responded, resulting in a ratio of 1:3.5. Baseline characteristics are shown in Table I. In addition to the completed questionnaires, we received numerous personal reactions from HS patients who made clear that they still struggle with recognition and understanding of their disease.

Sexual Health

Female Sexual Function Index

The mean FSFI score was 21.6 ± 9.6. Sexual dysfunction (FSFI ≤ 26.55) was found in 62% of the female patients. The presence of anogenital involvement (AGI) did not influence the FSFI score (AGI: 21.7 ± 9.1 vs no AGI: 21.6 ± 9.9; $P = 0.95$). The FSFI scores of sexually active patients in a relationship (SAPIR) (25.6 ± 6.3) were not different from sexually active patients not in a relationship (SAPNIR) (24.9 ± 7.9; $P = 0.56$). The FSFI score and age of onset showed a negative correlation ($r = -0.252$, $P < 0.001$), indicating that patients with a later age of onset of HS had worse sexual function. A negative correlation was also present between the FSFI score and DLQI score (without question 9, concerning sexual difficulties) ($r = -0.194$, $P = 0.003$), indicating that poor sexual health associates with poor QoL. No association was found between the FSFI score and duration of disease, VAS pain score, PtGA score or Hurley stage.

International Index of Erectile Function

The mean IIEF-total score was 49.7 ± 20.7, and the IIEF erectile function domain score was 20.6 ± 9.7. The presence of AGI and having a relationship did not significantly influence the IIEF-total score (AGI: 54.4 ± 17.6 vs no AGI: 46.6 ± 22.1; $P = 0.14$) (SAPIR: 57.2 ± 16.5 vs SAPNIR: 45.6 ± 25.6; $P = 0.09$). No association was found between the IIEF-total score and age of onset, disease duration, VAS pain score, PtGA score, Hurley stage or DLQI score.

Arizona Sexual Experience scale

The mean ASEX score was 16.7 ± 5.3. The criteria of sexual dysfunction were met by 42% of the patients. The ASEX score was significantly higher in women than in men (17.4 ± 5.2 vs 14.0 ± 4.7; $P < 0.001$) indicating that women experienced a more impaired sexual health. The presence of AGI or having a relationship did not significantly influence the ASEX score (AGI: 16.4 ± 5.0 vs no AGI: 16.9 ± 5.4; $P = 0.39$) (SAPIR: 15.5 ± 4.3 vs SAPNIR: 15.3 ± 4.8; $P = 0.87$). In women, there was a positive correlation between the ASEX score

and age of onset (r = 0.254, $P < 0.001$), indicating that females who were older at onset of HS had worse sexual function. This correlation was not observed in men (r = 0.025, $P = 0.85$). No association was found between the ASEX score and DLQI (for women and men separately), disease duration, VAS pain score, PtGA score or Hurley stage.

Quality of life

Dermatology Life Quality Index

The mean DLQI score was 12.5 ± 7.5. There was no significant difference in DLQI score between women and men (12.8 ± 7.5 vs 11.7 ± 7.4; $P = 0.33$). The presence of AGI significantly influenced the DLQI score (AGI: 14.1 ± 7.4 vs no AGI: 11.5 ± 7.4; $P = 0.003$). The DLQI score did not differ between patients in a relationship compared with patients not in a relationship (12.4 ± 7.4 vs 12.9 ± 7.8; $P = 0.60$). The DLQI score showed a significant positive correlation with VAS pain score (r = 0.667, $P < 0.001$), PtGA score ($r_s = 0.503$, $P < 0.001$) and Hurley stage ($r_s = 0.502$, $P < 0.001$), indicating that patients with severe disease had worse QoL. Also a negative correlation was observed between the DLQI score and age of onset (r = -0.147, $P = 0.01$), indicating that low QoL was associated with young age of disease onset. No association was found between the DLQI score and disease duration. The outcomes of DLQI item 9 are displayed in Table II.

Table II. DLQI item 9: 'Over the last week, how much has your skin caused any sexual difficulties?'

Answer options:	*n*	*%*
Not at all	60	20.0
A little	104	34.7
A lot	61	20.3
Very much	44	14.7
Not relevant	31	10.3

DLQI - Dermatology Life Quality Index

Disease activity

Patients with active disease had significantly higher DLQI scores and lower FSFI scores than patients without active disease (DLQI: 12.5 ± 7.5 vs 4.8 ± 4.7; $P < 0.001$) (FSFI: 21.6 ± 9.6 vs 27.9 ± 8.5; $P = 0.01$). The IIEF score and ASEX score did not differ between patients with or without active disease (IIEF: 49.7 ± 20.7 vs 33.3 ± 25.9; $P = 0.06$, ASEX: 16.7 ± 5.3 vs 15.2 ± 5.0; $P = 0.17$).

Decline in sexual activity after onset of hidradenitis suppurativa

In total, 179 of the 300 patients (59.7%) indicated that their sexual activity had declined after disease onset. The factors associated with this decline in sexual activity are displayed in Table III.

Table III. Decline of sexual activity after onset of disease

"To what extent do the following items have influence on your sexual health?"

	Never n (%)	**Sometimes** n (%)	**Often** n (%)	**Always** n (%)
Influence on physical appearance				
- Men	8 (21)	18 (47)	6 (16)	6 (16)
- Women	16 (11)	35 (25)	47 (33)	43 (31)
Fear of partner for contagiousness				
- Men	25 (66)	8 (21)	3 (8)	2 (5)
- Women	107 (76)	22 (16)	7 (5)	5 (4)
Fear of passing HS on to children				
- Men	28 (74)	5 (13)	4 (11)	1 (3)
- Women	69 (49)	21 (15)	27 (19)	24 (17)
Diminished sexual desire of patient				
- Men	5 (13)	18 (47)	11 (29)	4 (11)
- Women	13 (9)	43 (31)	64 (45)	21 (15)
Diminished sexual desire of partner				
- Men	15 (40)	15 (40)	5 (13)	3 (8)
- Women	72 (51)	45 (32)	15 (11)	9 (6)
Inconvenience caused by inflammation of the skin				
- Men	4 (11)	12 (32)	15 (40)	7 (18)
- Women	2 (1)	18 (13)	66 (47)	55 (39)
Inconvenience caused by medication				
- Men	25 (66)	8 (21)	4 (11)	1 (3)
- Women	52 (37)	44 (31)	26 (18)	19 (14)

Attention given to sexual health

The answers to the questions about attention given to sexual health by doctors are displayed in Table IV. Almost half of the patients indicated that the doctor did not give enough attention towards sexual problems, and a third of the patients stated that doctors should pay more attention to sexual problems.

Table IV. Attention given to sexual problems

	n	%
'Doctors give enough attention to sexual problems'		
- Yes	18	6
- No	132	44
- Unknown	150	50
'Doctors should give more attention to sexual problems'		
- Yes	101	34
- No	88	29
- Unknown	111	37

DISCUSSION

In this multicenter cross-sectional study we investigated sexual health and QoL in a substantial group of patients with HS. The group of patients was representative for the general HS population in terms of gender and disease characteristics.[2]

The results show that HS has a major impact on sexual health and QoL. Compared with sexual health scores of healthy females as known from the literature (FSFI 31.2 ± 3.9, ASEX 13.5 ± 3.9), the scores of our HS patients (FSFI 21.6 ± 9.6, ASEX 17.4 ± 5.2) were worse.[20,23] Similarly, the sexual health scores of the male patients (IIEF 49.7 ± 20.7, ASEX 14.0 ± 4.7) were worse than scores of healthy males (IIEF 54.5 ± 13.6, ASEX 13.5 ± 3.9), and a high number of our patients had erectile dysfunction.[23,26] The DLQI score of 12.5 ± 7.5 indicates that HS has a very large impact on the patients' QoL.[25] Our data were compatible with the findings of Kurek *et al.,*[15] who found a FSFI score of 22.1 ± 10.2 and IIEF score of 42.6 ± 27.1 in patients with HS.

AGI and disease severity did not influence sexual health in HS. However, the majority of the women stated that their sexual health declined because of the influence of HS on their physical appearance. As the physical symptoms of HS cannot completely explain the impaired sexual health in HS, we presume that psychological factors also play a role. The association between QoL and sexual health in women supports this hypothesis. Unlike sexual health, the QoL was negatively influenced by AGI, disease severity and disease activity. These findings are in line with those of previous studies.[6,7,9,10]

We found that age of onset influenced sexual health and QoL. Interestingly, female patients with an older age of onset had poorer sexual functioning than females with a young age of onset. This might be because HS patients have to make adjustments to their sexual life when HS starts after they became sexually active.[13] Our observation that patients with younger age of onset had a poorer QoL is in line with earlier findings, and probably results from a negative correlation between age at disease onset and disease severity.[8,9]

Sexual health was associated with QoL in women but not in men. This gender difference may result from the fact that intimate body regions are more frequently affected in women than in men.[15] Moreover, we found a higher impairment of sexual health in women, probably because they have a higher emotional and neuroendocrine responsiveness.[15]

In order to give a wider context to the results, a comparison between HS and psoriasis is made. It is known that the impact of psoriasis on the QoL is as large as the impact of diabetes, cancer and heart disease;[27] also, psoriasis has a considerable effect on sexual health.[28] HS and psoriasis have similar effects on sexual health,[28,29] although DLQI scores from patients with psoriasis (6.3-7.5) indicate the QoL is lower in HS than in psoriasis.[28,30–32] Finally, similar to HS, it seems that there is no relation between disease severity or AGI and sexual health in psoriasis.[28]

Only a small number of patients experienced sufficient attention from clinicians for their sexual problems. The fact that clinicians remain reluctant to address sexual problems could be explained by unawareness, shame, the complexity of sexual problems, difficulty in treatment and limited time.[33]

Our study has some limitations. First, the sexual health questionnaires are not validated for patients with chronic skin diseases. Second, with a response rate of 36%, there is a chance for selection bias. The low response rate is probably caused by the intimate nature of the questions.[28] However, since our patients characteristic were comparable to previous HS populations, it is possible to extrapolate our findings to the general HS population.[2]

In summary, this study demonstrates that HS has a major impact on sexual health and QoL. Sexual health is associated with QoL in women but not in men. Impairment in sexual health is associated with female gender and late onset of the disease. Early disease onset, disease activity and disease severity were important risk factors for impairment of QoL. The clinician should treat HS early and aggressively in an attempt to prevent permanent physical impairment. Furthermore, clinicians should discuss sexual function with HS patients, and offer them psychological intervention.

ACKNOWLEDGMENTS

The authors would like to thank R.W. Houwing (Department of Dermatology, Deventer Hospital) for informing the Deventer HS patients about this research.

REFERENCES

1 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

2 Schrader AMR, Deckers IE, van der Zee HH, *et al.* Hidradenitis suppurativa: A retrospective study of 846 Dutch patients to identify factors associated with disease severity. *J Am Acad Dermatol* 2014; **71**: 460–467.

3 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

4 Vazquez BG, Alikhan A, Weaver AL, *et al.* Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol* 2013; **133**: 97–103.

5 Canoui-Poitrine F, Le Thuaut A, Revuz JE, *et al.* Identification of three hidradenitis suppurativa phenotypes: Latent class analysis of a cross-sectional study. *J Invest Dermatol* 2013; **133**: 1506–1511.

6 Onderdijk AJ, van der Zee HH, Esmann S, *et al.* Depression in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2013; **27**: 473–478.

7 Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol* 2010; **90**: 264–268.

8 Von der Werth JM, Jemec GBE. Morbidity in patients with hidradenitis suppurativa. *Br J Dermatol* 2001; **144**: 809–813.

9 Wolkenstein P, Loundou A, Barrau K, *et al.* Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. *J Am Acad Dermatol* 2007; **56**: 621–623.

10 Alavi A, Anooshirvani N, Kim WB, *et al.* Quality-of-life impairment in patients with hidradenitis suppurativa: A canadian study. *Am J Clin Dermatol* 2015; **16**: 61–65.

11 Vinding GR, Knudsen KM, Ellervik C, *et al.* Self-reported skin morbidities and health-related quality of life: a population-based nested case-control study. *Dermatology* 2014; **228**: 261–268.

12 Arrington R, Cofrancesco J, Wu AW. Questionnaires to measure sexual quality of life. *Qual Life Res* 2004; **13**: 1643–1658.

13 Verschuren JEA, Enzlin P, Dijkstra PU, *et al.* Chronic disease and sexuality: a generic conceptual framework. *J Sex Res* 2010; **47**: 153–170.

14 DeRogatis LR. Assessment of sexual function/dysfunction via patient reported outcomes. *Int J Impot Res* 2008; **20**: 35–44.

15 Kurek A, Peters EMJ, Chanwangpong A, *et al.* Profound disturbances of sexual health in patients with acne inversa. *J Am Acad Dermatol* 2012; **67**: 422–428.

16 Http://www.hidradenitis.nl/. [homepage on the Internet].

17 Deckers IE, Mihajlović D, Prens E, *et al.* Hidradenitis suppurativa: a pilot study to determine patients capability to self-assess their Hurley stage. *Br J Dermatol* 2015; **172**: 1418–1419.

18 Rosen R, Brown C, Heiman J, *et al.* The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; **26**: 191–208.

19 Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther* 2005; **31**: 1–20.

20 Ter Kuile MM, Brauer M, Laan E. The female sexual function index (FSFI) and the female sexual distress scale (FSDS): psychometric properties within a Dutch population. *J Sex Marital Ther* 2006; **32**: 289–304.

21 Rosen RC, Riley A, Wagner G, *et al.* The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–830.

22 Cappelleri JC, Rosen RC, Smith MD, *et al.* Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology* 1999; **54**: 346–351.

23 McGahuey CA, Gelenberg AJ, Laukes CA, *et al.* The Arizona sexual experience scale (ASEX): reliability and validity. *J Sex Marital Ther* 2000; **26**: 25–40.

24 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.

25 Hongbo Y, Thomas CL, Harrison MA, *et al.* Translating the science of quality of life into practice: What do dermatology Life Quality Index Scores Mean? *J Invest Dermatol* 2005; **125**: 659–664.

26 Lim TO, Das A, Rampal S, *et al.* Cross-cultural adaptation and validation of the English version of the International Index of Erectile Function (IIEF) for use in Malaysia. *Int J Impot Res* 2003; **15**: 329–336.

27 Rapp SR, Feldman SR, Exum ML, *et al.* Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999; **41**: 401–407.

28 Meeuwis KAP, De Hullu JA, Van de Nieuwenhof HP, *et al.* Quality of life and sexual health in patients with genital psoriasis. *Br J Dermatol* 2011; **164**: 1247–1255.

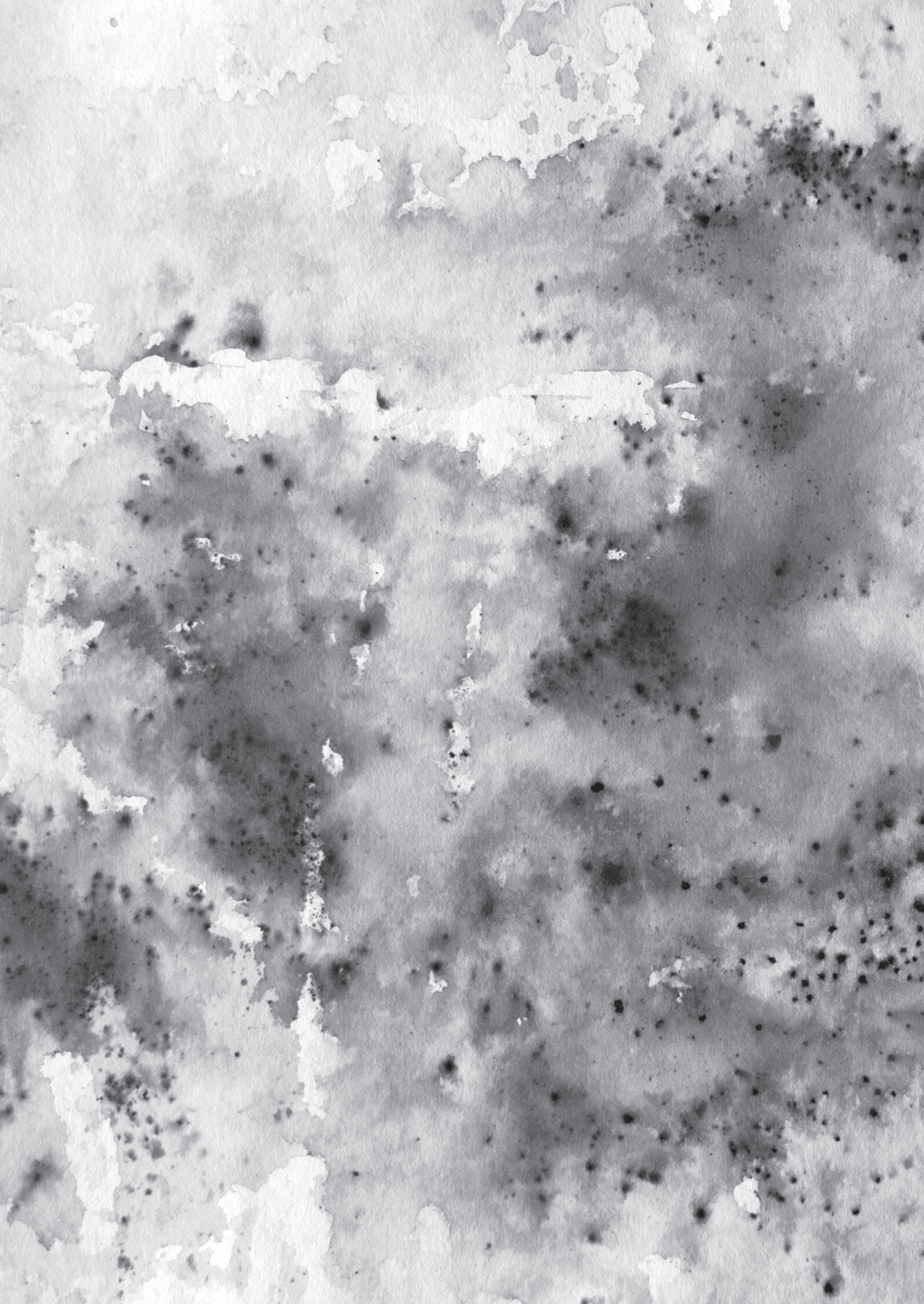
29 Mercan S, Altunay IK, Demir B, *et al.* Sexual dysfunctions in patients with neurodermatitis and psoriasis. *J Sex Marital Ther* 2008; **34**: 160–168.

30 Goulding JMR, Price CL, Defty CL, *et al.* Erectile dysfunction in patients with psoriasis: increased prevalence, an unmet need, and a chance to intervene. *Br J Dermatol* 2011; **164**: 103–109.

31 Herédi E, Rencz F, Balogh O, *et al.* Exploring the relationship between EQ-5D, DLQI and PASI, and mapping EQ-5D utilities: a cross-sectional study in psoriasis from Hungary. *Eur J Health Econ* 2014; **15**: 111–119.

32 De Korte J, Van Onselen J, Kownacki S, *et al.* Quality of care in patients with psoriasis: an initial clinical study of an international disease management programme. *J Eur Acad Dermatol Venereol* 2005; **19**: 35–41.

33 Nusbaum MR, Hamilton C, Lenahan P. Chronic illness and sexual functioning. *Am Fam Physician* 2003; **67**: 347–354.



Chapter 8

Hidradenitis suppurativa is associated with a low socioeconomic status: a cross-sectional reference study

Inge E. Deckers, Ineke C. Janse, Hessel H. van der Zee, Tamar E.C. Nijsten, Jurr Boer, Barbara Horváth, Errol P. Prens

Submitted for publication

ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic debilitating disease, whereby school attendance and employment can be disturbed.

Objective: To determine the socioeconomic status (SES) in patients with HS relative to dermatological patients, and whether specific clinical HS characteristics correlate with SES.

Methods: For this multicenter cross-sectional study, data were collected of patients with HS and sex and age matched dermatological patients in a 1:2 ratio. SES was derived from the mean household income and real estate value on a neighborhood level. Univariable and multivariable ordinal logistic regression were used to determine if clinical characteristics were associated with SES in patients with HS.

Results: The SES distribution among 1,018 HS patients was significantly lower (low SES: 46.4%, medium SES: 39.0%, high SES: 14.6%), than among 2,039 age and sex matched dermatological control patients (low SES: 34.3%, medium SES: 40.1%, high SES: 25.6%; $P < 0.001$). In HS patients a low SES was associated with axillary involvement (OR 1.42, 95% CI 1.02-1.99), high body mass index (OR 1.03, 95% CI 1.01-1.06) and lower current age (OR 0.98, 95% CI 0.97-0.99), but not with diseases severity or age of onset, in the multivariable logistic regression.

Limitations: SES was based on postal code level and causality cannot be determined.

Conclusion: Patients with HS have a significant lower SES than other dermatological patients. Low SES was associated with obesity, but not with disease severity. Since low SES is associated with an unhealthy lifestyle such as smoking and obesity, low SES might be a risk factor for developing HS.

INTRODUCTION

Hidradenitis suppurativa (HS), is a chronic skin disease, characterized by painful deep-seated nodules or abscesses mainly located at the axillary, inguinal and anogenital area.[1,2] The prevalence of HS ranges between 0.05% and 4%, and women are more frequently affected than men.[1,3,4] Smoking and obesity are not only suggested as risk factors for the development of HS, but are also associated with disease severity.[5,6] To date there is no cure for HS, and patients are often treated with long-term antibiotics or in more severe cases with biologics; generally, surgery is needed to induce remmision.[3]

It is not surprising that the combination of chronic painful lesions and a lack of a definite cure, leads to a diminished quality of life (QoL). Compared with patients with other dermatological diseases, patients with HS have the lowest QoL.[7,8] There are conflicting results on the impact of HS on work ability. Matusiak *et al*.[9] showed that HS patients miss on average 33.6 workdays per year because of their HS. They even suggested that of their cohort of 30 patients, seven did not get a promotion and three lost their jobs because of HS.[9] However, two other studies showed that HS patients missed only 2 to 3 workdays per year.[7,10]

The clinical impression is that patients with HS have a lower socioeconomic status (SES) than other dermatological patients. It has been suggested that HS disrupts school attendance and employment.[11] However, previous studies showed that 60-80% of HS patients had secondary or tertiary education level,[4,10,12] but in only one study a control group was available. To the best of our knowledge, no studies have been performed in which the income or real estate value were used to determine the SES in HS.

The primary aim of this study was to determine the SES of patients with HS and a control group of patients with common skin diseases. SES was based on the mean household income and the mean real estate value per postal code area. The secondary aim was to determine if specific clinical HS characteristics were associated with a lower SES; this in order to get an impression whether HS is a risk factor for lower SES.

METHODS

The Departments of Dermatology at Erasmus University Medical Center Rotterdam, Deventer Hospital, and University Medical Center Groningen, The Netherlands have a special interest in HS. Between 2007 and 2015 data were collected of 1,059 HS patients. All patients were diagnosed by a dermatologist; the diagnosis was based on patients' history of HS symptoms and on physical examination.[1,2] Of these HS patients, the six digit postal codes were collected. In addition, postal codes were collected of a sex and age distribution matched dermatological control group in a 1:2 ratio (Supplement Table I).

The medical ethical review board of the Erasmus University Medical Center Rotterdam has reviewed and approved the protocol under number MEC-2014-230.

Socioeconomic status

The SES was based on an indicator developed by Statistics Netherlands (*Centraal Bureau van de Statistiek)*.[13] Statistics Netherlands is an autonomous agency, and has the task to carry out statistical research for the Dutch government for practice, policy and research purposes.[14] On a neighborhood level, based on the six-digit postal code, the most recent mean household income after tax and mean real estate value were determined (both from 2013). These data were available at Statistics Netherlands and were collected by the Dutch tax authorities. On average a six-digit postal code comprises data from 17 households, providing a small enough sample to obtain an accurate impression of the SES in that neighborhood.[13] The household income and real estate value had to be combined into one variable that could be used as a representative of SES. This was done using principal component analysis, in which the mean household income and the mean real estate value per postal code area were equally included.[13] Hereafter this combined variable was categorized in three groups, namely 1st to 3rd deciles for low SES, 4th to 7th deciles for medium SES and 8th to 10th deciles for high SES.[15] This method has been shown to be a valid predictor of SES, and to be valid for ten years before and after the reference year (2013).[15,16]

Data collection of patients with hidradenitis suppurativa

Additional data were collected from the medical files of the patients with HS, e.g. age of onset of HS, family history of HS (first- or second-degree family member affected), the body regions affected by HS and smoking status. The body mass index (BMI) was calculated based on reported body weight and height. Disease severity was assessed using the Hurley classification of the worst location affected.[2]

Dermatological control patients

This SES indicator was known to be only reliable when compared with an age comparable group.[13] Therefore we have chosen sex and age matched controls to make comparisons of the SES. For every center, control patients were frequency matched on a 1:2 ratio (Supplement Table I). Because of the chronic nature of HS, we chose mostly patients with chronic skin diseases, such as eczema and psoriasis, but also data of patients with other dermatological diseases were collected (Supplement Table II).

Statistical analysis

Statistical analysis was performed using SPSS version 21 (IBM Corp, Armonk, NY). A chi-square test was used to answer the primary research question, presented as number (n)

with their corresponding percentage. Independent *t*-tests were performed for nominal data, presented as mean ± standard deviation (SD). As a subgroup analysis the specific dermatological control diseases were compared with the HS group. A *P*-value less than 0.05 was considered statistically significant. As a secondary step we determined whether patients- or disease characteristics were risk factors for a lower SES among patients with HS. Twelve out of the 13 tests of parallel lines were nonsignificant and therefore an ordinal logistic regression model was applied. Based on clinical expertise and the literature, candidate predictors were included (Table III). First univariable ordinal logistic regression was performed, with SES as the dependent variable, in which a significant odds ratio (OR) > 1 is a predictor for low SES. Hereafter in the multivariable model, all variables were included to observe if patient- and disease characteristics were independent predictors of SES. In order to prevent overfitting, a maximum of 49 degrees of freedom could be spent based on the sample sizes of the SES distribution among HS patients (Table I).[17] Data are presented as OR with the 95% confidence interval (CI). Proportional ORs were obtained on the three levels of SES, and should be interpreted as follows: a significant OR of 2 indicates that the odds of low SES are twice as high as medium and high SES combined. Missing values of the patients' and disease characteristics were included in the univariable and multivariable model.

RESULTS

Data were collected from 1,059 HS patients and 2,088 age and sex matched dermatological control patients. Because of invalid or irretrievable addresses, 28 HS patients were excluded. In addition, 13 HS patients and 49 control patients were excluded because of missing data on SES (mean income or real estate value missing for the corresponding postal code). In total 1018 HS patients (mean age 38.7 ± 12.7 and 71.7% female) and 2039 dermatological control patients were analyzed (Table I and Supplement Table I). The control group consisted mostly of eczema patients (n=708), psoriasis (n=549), naevi (n=327), skin cancer (n=141) and a rest group (n=314) of combined diseases (Supplement Table II).

Patients with hidradenitis suppurativa have a significant lower socioeconomic status

Of the patients with HS 46.4% had a low SES, 39.0% a medium SES and 14.6% a high SES; this is lower than the SES of the general Dutch population (30% low SES, 40% medium SES and 30% high SES by definition). The SES of HS patients was significantly lower than that of the age and sex matched dermatological control group (34.3% low SES, 40.1% medium SES, and 25.6% high SES, $P < 0.001$) (Table I). In addition, in a subgroup analysis

for the specific dermatological control diseases, HS had the lowest SES, followed by psoriasis and eczema, whereas patients with skin cancer had the highest SES (Figure 1).

Table I. Socioeconomic status and general characteristics of patients with hidradenitis suppurativa and other dermatological control patients

	Hidradenitis suppurativa (n=1018)	**Control dermatological diseases**[a] (n=2039)	***P*-value**[b]
Gender, n (%)			
- Female	730 (71.7)	1464 (71.8)	0.96
- Male	288 (28.3)	575 (28.2)	
Age years, mean ± SD	38.7 ± 12.7	38.9 ± 13.3	0.64
Socioeconomic status,[c] n (%)			
- Low SES	472 (46.4)	699 (34.3)	**< 0.001**
- Medium SES	397 (39.0)	817 (40.1)	
- High SES	149 (14.6)	523 (25.6)	

[a] Control dermatological diseases: e.g. eczema, psoriasis, naevi and skin cancer (Supplement Table II)
[b] *t*-test for nominal data and chi-square test for categorical data
[c] Socioeconomic status (SES) was based on mean household income and real estate value per postal code area, which were on national level divided in low SES (1st to 3rd deciles), medium SES (4th to 7th deciles) and high SES (8th to 10th deciles)[13]

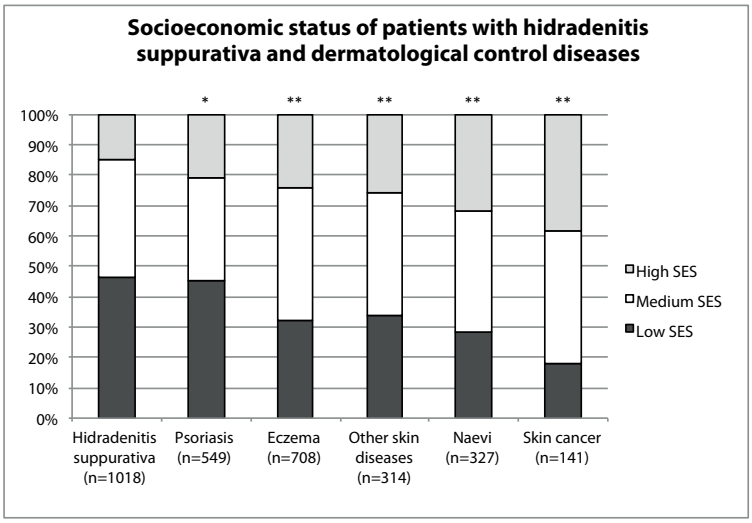


Figure 1. Socioeconomic status (SES) of hidradenitis suppurativa and control dermatologic diseases. Hidradenitis suppurativa showed to have the lowest SES of every skin disease when compared using chi-square test. The asterix shows the *P*-value of the comparison of hidradenitis suppurativa with the corresponding skin disease; * $P = 0.005$ and ** $P < 0.001$.

Axillary involvement, age and BMI are indicators for lower socioeconomic status in patients with hidradenitis suppurativa

Affection of the axillary region was the only disease characteristic associated with a lower SES, with 69.5% of the low SES patients having axillary involvement versus 51.0% of the high SES patients (OR 1.42, 95% CI 1.03-1.99; P = 0.04) (Table II and III). None of the other body regions showed a relation with SES. Patients with low SES were more

Table II. Patient and disease characteristics of hidradenitis suppurativa for every socioeconomic status[a]

	Low SES (n=472)	**Medium SES** (n=397)	**High SES** (n=149)
Gender, n (%)			
- Female	332 (70.3)	297 (74.8)	101 (67.8)
- Male	140 (29.7)	100 (25.2)	48 (32.2)
Age years, mean ± SD	37.4 ± 12.5	39.4 ± 12.7	40.9 ± 13.1
Age of disease onset years, mean ± SD	23.4 ± 10.5	23.8 ± 10.8	25.7 ± 12.8
Family history, n (%)			
- Positive	173 (41.2)	125 (34.8)	49 (35.5)
Hurley stage, n (%)			
- Hurley I	212 (44.9)	166 (41.8)	64 (43.0)
- Hurley II	208 (44.1)	190 (47.9)	64 (43.0)
- Hurley III	52 (11.0)	41 (10.3)	21 (14.0)
Body region affected, n (%)			
- Axillary	326 (69.5)	251 (63.4)	76 (51.0)
- Inguinal/femoral	404 (86.1)	345 (87.1)	122 (81.9)
- Genital	146 (31.1)	125 (31.6)	40 (26.8)
- Gluteal/perianal	223 (47.5)	186 (47.0)	77 (51.7)
- Other[b]	178 (38.0)	142 (35.9)	49 (32.9)
No. of body sites affected, n (%)			
- 1-2 sites	206 (44.0)	188 (47.5)	81 (54.4)
- 3-5 sites	262 (56.0)	208 (52.5)	68 (45.6)
BMI kg/m^2, mean ± SD	28.4 ± 6.4	27.9 ± 5.7	26.3 ± 4.6
BMI subgroups,[c] n (%)			
- Normal	161 (35.2)	134 (34.7)	62 (44.3)
- Overweight	128 (28.0)	134 (34.7)	56 (40.0)
- Obese	168 (36.8)	118 (30.6)	22 (15.7)
Smoking status, n (%)			
- Active smoker	341 (73.3)	280 (71.4)	94 (64.0)
- Ex-smoker	47 (10.1)	63 (16.1)	24 (16.3)
- Nonsmoker	77 (16.6)	49 (12.5)	29 (19.7)

BMI - body mass index; SES - socioeconomic status

[a] SES was based on mean household income and real estate value per postal code area, which were on national level divided in low SES (1st to 3rd deciles), medium SES (4th to 7th deciles) and high SES (8th to 10th deciles)[13]

[b] Other: mammary region, abdominal region or atypical regions affected

[c] Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

often affected at more body regions in the univariable analysis, but this did not remain significant in the multivariable analysis. In the uni- and multivariable analysis, there was no difference in distribution of SES across different categories of disease severity according to Hurley, family history of HS or age of disease onset.

BMI and age also showed to be associated with SES (Table II and III). The mean BMI was higher in the low SES group than in the high SES group (mean BMI 28.4 ± 6.4 vs 26.3 ± 4.6; OR 1.03, 95% CI 1.01-1.06; *P* = 0.003). Also in the low SES group 36.8% of the patients with HS were obese versus 15.7% of the high SES patients. Patients were older in the high SES group (40.9 ± 13.1 years) than in the low SES group (37.4 ± 12.5 years; OR 0.98, 95% CI 0.97-0.99; *P* = 0.001). Among HS patients, smoking status showed no relation with SES.

Table III. Univariable and multivariable analysis of factors associated with socioeconomic status in hidradenitis suppurativa

	Univariable[a] (n=1018)		**Multivariable**[a] (n=1018)	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Gender, ref. male				
- Female	0.96 (0.74-1.24)	0.75	0.90 (0.67-1.20)	0.47
Age years	**0.98 (0.98-0.99)**	**0.001**	**0.98 (0.97-0.99)**	**0.001**
Age of disease onset years	0.99 (0.98-1.00)	0.06	1.01 (0.99-1.02)	0.24
Family history, ref. no				
- Positive	1.26 (0.98-1.62)	0.08	1.27 (0.96-1.67)	0.09
Hurley stage, ref. Hurley I				
- Hurley II	0.93 (0.72-1.18)	0.54	0.86 (0.66-1.12)	0.25
- Hurley III	0.86 (0.58-1.28)	0.45	0.91 (0.59-1.41)	0.68
Body region affected, ref. not affected				
- Axillary	**1.62 (1.27-2.07)**	**<0.001**	**1.42 (1.02-1.99)**	**0.04**
- Inguinal/femoral	1.13 (0.81-1.59)	0.47	1.17 (0.78-1.77)	0.44
- Genital	1.08 (0.84-1.40)	0.53	1.17 (0.86-1.59)	0.33
- Gluteal/perianal	0.94 (0.74-1.18)	0.59	0.86 (0.62-1.20)	0.38
- Other	1.15 (0.90-1.47)	0.25	0.87 (0.63-1.20)	0.40
No. of body sites affected, ref. 1-2				
- 3-5 sites	**1.28 (1.01-1.62)**	**0.04**	1.19 (0.73-1.93)	0.49
BMI kg/m^2	**1.03 (1.01-1.05)**	**0.002**	**1.03 (1.01-1.06)**	**0.003**
Smoking status, ref. nonsmoker				
- Active smoker	1.05 (0.75-1.46)	0.79	1.22 (0.84-1.76)	0.29
- Ex-smoker	0.66 (0.43-1.02)	0.06	0.78 (0.49-1.25)	0.31

BMI - body mass index; OR - odds ratio; CI - confidence interval

[a] Ordinal logistic regression analysis with socioeconomic status as dependent variable: univariable model, unadjusted; and multivariable model, adjusted for factors and covariates in the model (OR>1 is a predictor for low socioeconomic status)

DISCUSSION

This multicenter cross-sectional study shows that patients with HS have a lower SES than the general Dutch population, and age and sex matched dermatological patients. In a representative sample of the population 30% would have a low SES, 40% a medium SES and 30% a high SES;[15] however, in our HS population 46% had a low SES and only 15% a high SES. For our control group we chose mostly patients with psoriasis and eczema, because these are also chronic skin diseases that affect young people and have a high disease burden.[18–20] Although 45% of the patients with psoriasis and 32% of the patients with eczema had a low SES; in the direct comparison, the SES of patients with HS remained significantly lower (Figure 1). Patients with naevi had a SES comparable with the general population, whereas our results confirm that patients with skin cancer have a higher SES.[15,21] As expected, older patients with HS had a higher SES. In general, with increasing age people have a higher income and are able to afford more expensive real estates.[13] Therefore an age and sex matched control group was used to make SES comparisons.

The secondary aim of this study was to investigate if specific patient or disease characteristics were associated with the SES. We anticipated that if HS would lead to a lower SES, patients with a more severe disease would have a lower SES because of the inability to perform their jobs or frequent sick leave.[9] However, we did not find a difference in Hurley stage distribution among the SES groups. Low SES was associated with more affected body regions in the univariable analysis but not in the multivariable model. Only axillary involvement showed a relation with low SES, but this relationship could not be observed for any other body region affected by HS.

We hypothesized that if a lower SES is a consequence of HS, patients with a young age of onset might have a lower SES, because of missed education or job opportunities. However, there was no difference in age of onset between the different SES groups. Also previous studies reported that 60-80% of the patients had secondary or tertiary education (high school, college or university).[4,10,12] However, education level alone is not reliable for determining SES, because there is only a modest correlation between education level and income.[22] In addition, the number of workdays missed by HS patients seems limited.[7,10] Therefore it could be possible that the lower SES was pre-existent to HS.

We observed that HS patients with a low SES were more often obese than HS patients with a high SES. In a European study, people from low SES neighborhoods were shown to have a higher BMI.[23] Inhabitants from these neighborhoods also showed more obesity-related behavior, such as eating less fruit and vegetables, whereas they drank more beverages with a high sugar content.[23] In the general population smoking is also associated low SES.[23–26] Since both smoking and obesity are risk factors for HS, it could be that people with a low SES have a higher risk of developing HS;[5,6] but because of

the cross-sectional study design we were unable to confirm causality. The only way to properly investigate causality is to set up a large prospective population-based study to determine which risk factors are causative for HS.

Another limitation of our study is the definition of SES. Ideally SES consists of personal income, education level and occupation.[22] For this study we used aggregated data on postal code level. Even though this postal code data showed to be a good predictor of individual SES,[13,15,16] it is possible that someone with a higher income lived in a low SES neighborhood or vice versa. Also SES differs across the Netherlands,[27] therefore we collected data from three hospitals that are located in different geographical areas. Since all three centers have special interest in HS, patients are referred from wide surrounding areas; therefore they cover a wide area of The Netherlands. However, two hospitals were tertiary referral centers, which might result in an overrepresentation of HS patients with severe disease.[6]

Concluding, this study shows that patients with HS have a significantly lower SES the general Dutch population and than other dermatological patients. We did not observe an association between SES and disease severity or age of onset. Therefore low SES may be an independent risk factor for HS, since unhealthy behavior such as smoking and obesity is more prevalent in people with low SES. A prospective cohort study is needed to determine causality.

ACKNOWLEDGMENTS

The authors thank C. van Duin and R. Blokzijl from Statistics Netherlands for their help with the SES indicator; L.M. Hollestein from the Department of Dermatology, Erasmus Medical Center, Rotterdam, for her help with the statistical analysis.

REFERENCES

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

2 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

3 Zouboulis CC, Desai N, Emtestam L, *et al.* European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; **29**: 619–644.

4 Vazquez BG, Alikhan A, Weaver AL, *et al.* Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol* 2013; **133**: 97–103.

5 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

6 Schrader AMR, Deckers IE, van der Zee HH, *et al.* Hidradenitis suppurativa: A retrospective study of 846 Dutch patients to identify factors associated with disease severity. *J Am Acad Dermatol* 2014; **71**: 460–467.

7 Onderdijk AJ, van der Zee HH, Esmann S, *et al.* Depression in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2013; **27**: 473–478.

8 Wolkenstein P, Loundou A, Barrau K, *et al.* Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. *J Am Acad Dermatol* 2007; **56**: 621–623.

9 Matusiak Ł, Bieniek A, Szepietowski JC. Hidradenitis suppurativa markedly decreases quality of life and professional activity. *J Am Acad Dermatol* 2010; **62**: 706–708.

10 Jemec GBE, Heidenheim M, Nielsen NH. Hidradenitis suppurativa-characteristics and consequences. *Clin Exp Dermatol* 1996; **21**: 419–423.

11 Jen M, Chang MW. Hidradenitis Suppurativa. In: Tom WL (ed) *Severe Skin Diseasse in Children*. Springer-Verlag Berlin Heidelberg. 2014: 53–63.

12 Bieniek A, Matusiak L, Okulewicz-Gojlik D, Szepietowski JC. Surgical treatment of hidradenitis suppurativa: experiences and recommendations. *Dermatol Surg* 2010; **36**: 1998–2004.

13 Van Duin C, Keij I. Sociaal-economische status indicator op postcode niveau. *Maandstatistiek van de Bevolking* 2002; **50**: 32–35.

14 Netherlands Statistics. Statistics Netherlands Act November 2003. 2004.

15 Van Hattem S, Aarts MJ, Louwman WJ, *et al.* Increase in basal cell carcinoma incidence steepest in individuals with high socioeconomic status: results of a cancer registry study in The Netherlands. *Br J Dermatol* 2009; **161**: 840–845.

16 Van Duin C, Keij I. Welvaartsongelijkheid in de jaarlijkse sterftekans. *Maandstatistiek van de Bevolking* 2002; **50**: 25–26.

17 Whitehead J. Sample size calculations for ordered categorical data. *Stat Med* 1993; **12**: 2257–2271.

18 Wahl A, Loge JH, Wiklund I, Hanestad BR. The burden of psoriasis: a study concerning health-related quality of life among Norwegian adult patients with psoriasis compared with general population norms. *J Am Acad Dermatol* 2000; **43**: 803–808.

19 Bingefors K, Lindberg M, Isacson D. Quality of life, use of topical medications and socio-economic data in hand eczema: a Swedish nationwide survey. *Acta Derm Venereol* 2011; **91**: 452–458.

20 Basra MKA, Fenech R, Gatt RM, *et al.* The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**: 997–1035.

21 Zell JA, Cinar P, Mobasher M, *et al.* Survival for patients with invasive cutaneous melanoma among ethnic groups: the effects of socioeconomic status and treatment. *J Clin Oncol* 2008; **26**: 66–75.

22 Braveman PA, Cubbin C, Egerter S, *et al.* Socioeconomic status in health research: one size does not fit all. *JAMA* 2005; **294**: 2879–2888.

23 Lakerveld J, Rebah M Ben, Mackenbach JD, *et al.* Obesity-related behaviours and BMI in five urban regions across Europe: sampling design and results from the SPOTLIGHT cross-sectional survey. *BMJ Open* 2015; **5**: e008505.

24 Adler NE, Boyce T, Chesney MA, *et al.* Socioeconomic status and health: the challenge of the gradient. *Am Psychol* 1994; **49**: 15–24.

25 Benson FE, Kuipers MAG, Nierkens V, *et al.* Socioeconomic inequalities in smoking in The Netherlands before and during the Global Financial Crisis: a repeated cross-sectional study. *BMC Public Health* 2015; **15**: 469.

26 Sobal J, Stunkard AJ. Socioeconomic status and obesity: a review of the literature. *Psychol Bull* 1989; **105**: 260–275.

27 Mulder M. Sociaaleconomische status 2010. *Volksgezondheid Toekomst Verkenning, Nationale Atlas Volksgezondheid. Bilthoven: RIVM* 2013; **12**.

Supplement Table I. General characteristics of patients with hidradenitis suppurativa and dermatological control patients per hospital

	Hidradenitis suppurativa	Control dermatological diseases[a]	*P*-value[b]
Erasmus Medical Center Rotterdam	(n=474)	(n=961)	
Gender, n (%)			
- Female	320 (67.5)	648 (67.4)	0.98
- Male	154 (32.5)	313 (32.6)	
Age years, mean ± SD	37.7 ± 13.1	37.4 ± 13.3	0.75
Deventer Hospital	(n=395)	(n=784)	
Gender, n (%)			
- Female	306 (77.5)	611 (77.9)	0.86
- Male	89 (22.5)	173 (22.1)	
Age years, mean ± SD	38.2 ± 12.1	39.1 ± 13.6	0.23
University Medical Center Groningen	(n=149)	(n=294)	
Gender, n (%)			
- Female	104 (69.8)	205 (69.7)	0.99
- Male	45 (30.2)	89 (30.3)	
Age years, mean ± SD	43.4 ± 11.9	43.3 ± 11.7	0.99

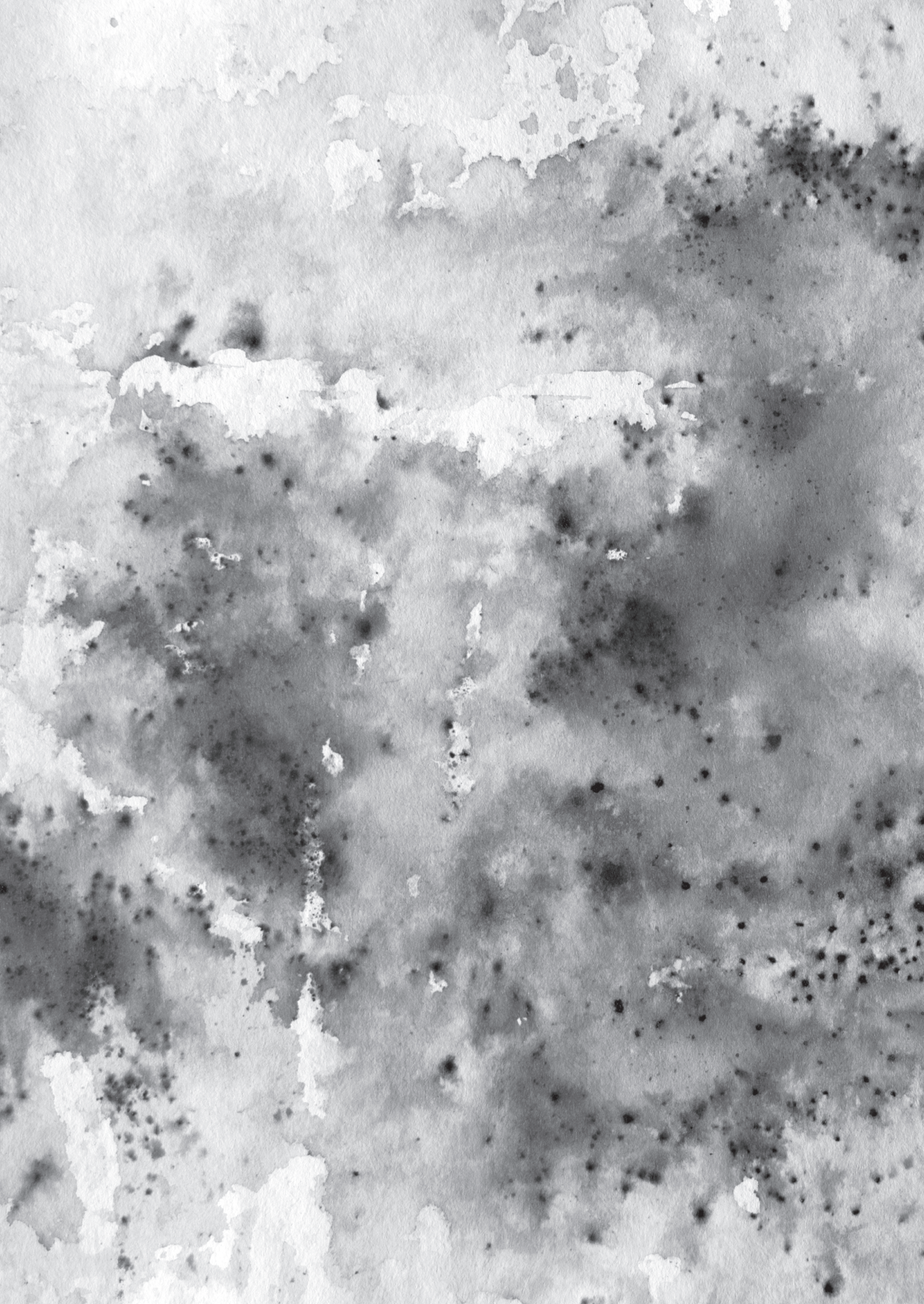
[a] Control dermatological diseases: e.g. eczema, psoriasis, naevi and skin cancer (Supplement Table II)
[b] *t*-test for nominal data and chi-square test for categorical data

Supplement Table II. Diagnoses of dermatological control patients

	n=2039
Eczema	708
Psoriasis	549
Naevi	327
Skin cancer	141
Other	
- Verruca	89
- Urticaria	46
- Varices	58
- Alopecia	31
- Rosacea	31
- Vitiligo	11
- Actinic keratosis	7
- Dermatomycosis	7
- Prurigo/pruritus	4
- Chronic discoid lupus erythematosus	3
- Condylomata	3
- Pityriasis versicolor	3
- Lichen planus/sclerosus	3
- Hyperhidrosis	3
- Dermatofibroma	3
- Bullous pemphigoid	2
- Ulcers	2
- Erythema migrans	1
- Purpura	1
- Deep venous thrombosis	1
- Lentigo solaris	1
- Hemangioma	1
- Sarcoidosis	1
- Perniones	1
- Xanthelasmata	1

Part IV

Treatments of Hidradenitis Suppurativa



Chapter 9

An update on medical treatment options for hidradenitis suppurativa

Inge E. Deckers, Errol P. Prens

Drugs. 2016;76:215-229

ABSTRACT

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent inflammatory nodules mostly located in the armpits and groin. Over the years multiple treatment options for HS have been proposed; however, to date a cure is still lacking. In this update we provide an overview of most drug treatments reported on for HS, where possible with their mode of action and side effects.

In mild cases, clindamycin lotion or resorcinol cream have proven effective. Tetracyclines are a first-line systemic option in more widespread or severe cases, followed by the combination of clindamycin with rifampicin. However, the recurrence rate is high after discontinuation of clindamycin plus rifampicin combination therapy. Long-term treatment with retinoids, especially acitretin is feasible, although teratogenicity has to be taken into account in females of reproductive age. Multiple anti-inflammatory drugs have been suggested for HS, such as dapsone, fumarates or cyclosporine. However, their effectiveness in HS is based on small case series with varying results. If most common treatments have failed, biologics (e.g. infliximab or adalimumab) are the next step. Although not addressed in this review, surgical interventions are often needed to achieve remission.

1. INTRODUCTION

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, recurrent inflammatory skin disease.[1,2] The diagnosis is based on the clinical presentation. Patients present with comedones, inflamed or non-inflamed nodules and abscesses, often followed by sinus tract formation and scarring. These lesions are generally present in the axillary, inguinal, pubic and gluteal area, and the infra-mammary area in female patients. To make the diagnosis, these painful or purulent nodules have to occur at least twice per six months.[3] The disease usually develops after puberty, when patients are in their early twenties. However, although rare, HS can also develop in children.[4,5] The disease has a prevalence ranging from 0.05% to 4%, and females are more often affected than males, with a female to male ratio of 3:1.[6–8] Disease severity can be assessed using different severity scores. The oldest and still most commonly used severity assessment is the Hurley score (Table I and Figure 1).[2,9] It is easy to use, but static and therefore less suitable for monitoring treatment efficacy. The Modified Sartorius Score is more dynamic. It is based on the number of areas involved and the number of nodules, fistulas and hypertrophic scars.[10,11] However, because of its comprehensiveness, it is time consuming, making it less suitable for daily practice. The Hidradenitis Suppurativa Physician Global Assess-

Table I. Hurley's classification for clinical staging of disease severity in hidradenitis suppurativa[2,9]

Stage	Description
I	Abscess formation, single or multiple, without sinus tracts and cicatrization
II	Recurrent abscesses with tract formation and cicatrization. Single or multiple separated lesions
III	Multiple interconnected tracts and abscesses throughout an entire anatomical area

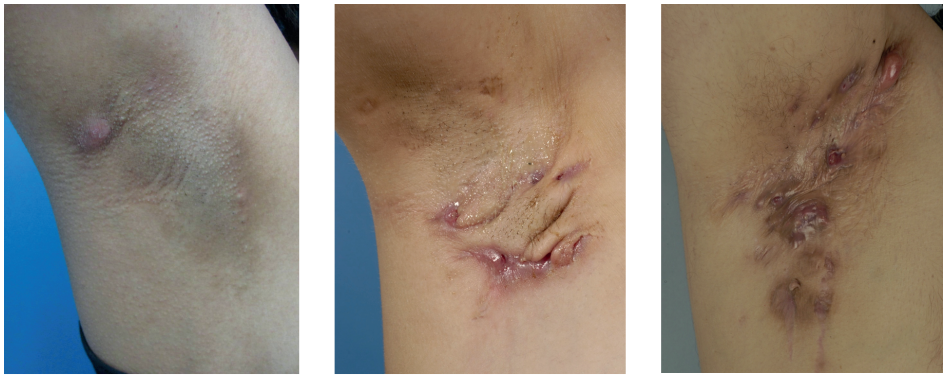


Figure 1. Clinical presentation of the three stages of disease severity of hidradenitis suppurativa according to Hurley.[2,9]

Table II. Physician's global assessment scale of hidradenitis suppurativa[a]

Clear	No inflammatory or noninflammatory nodules
Minimal	Only noninflammatory nodules
Mild	Less than five inflammatory nodules; **or** only one abscess or draining fistula present
Moderate	Five or more inflammatory nodules; **or** one abscess or draining fistula and at least one inflammatory nodule; **or** two to five abscesses or draining fistulas and less than ten inflammatory nodules
Severe	Two to five abscesses or draining fistulas and ten or more inflammatory nodules
Very severe	More than five abscesses or draining fistulas

[a] Adjusted physician's global assessment scale for hidradenitis suppurativa.[3,12]

ment (HS-PGA) score is suitable for observing change during treatment and is easy to use and validated,[3,12] therefore it is frequently used at present (Table II).

The pathogenesis of HS is still not fully understood. The primary event is thought to be infundibular hyperkeratosis and hyperplasia of the follicular epithelium causing occlusion of hair follicles.[13,14] This leads to accumulation of cellular debris and cyst formation, and eventually rupture of the hair follicle causing abscess formation and the development of sinus tracts and scarring.[15,16] The role of an aberrant immune response gets more attention in the pathogenesis of HS. Elevated levels of interleukin (IL)-1β, IL-10 and tumor necrosis factor alpha (TNF-α) have been found in lesional and perilesional skin.[17] Also overexpression of macrophages producing IL-12 and IL-23, and IL-17 producing cells were found in lesional HS skin.[18] These results were recently confirmed by Kelly *at al*.[19] They also demonstrated activated caspase-1 in HS skin, which is associated with IL-1β and IL-18 production. These results suggest that the IL-23/Th17 and the caspase-1 pathways play an important role in the pathogenesis of HS.[17–19]

To date, there is no medical cure for HS, and multiple treatments have been suggested for HS. Often a combination of drug treatment and surgical intervention is needed to achieve remission. Recently the European Guidelines for the treatment of HS have been published,[3] giving advice on the therapeutic steps to be taken in the treatment of HS. In this comprehensive review we will give an overview of most HS drug treatments with their mode of action. The commonly used antibiotics and biologics will be discussed, as will a few more experimental and future therapeutic options.

2. TOPICAL TREATMENTS

For mild HS, where only comedones, papules, pustules or inflammatory nodules are present, topical treatment, together with lifestyle advices, are often sufficient. The best results are achieved when a combination of a peeling cream, to resolve and prevent

follicular blockage, is given with a local antibiotic, as a topical anti-inflammatory agent and to prevent secondary infection.

2.1 Topical clindamycin

Topical clindamycin is a simple and widely used treatment for HS.[20] Daily topical application of clindamycin 1% proved more effective than placebo in a small double-blind study of patients with Hurley stage I and mild stage II HS. After three months of clindamycin application a significant reduction in pustules, inflammatory nodules and abscesses was observed. The only side effect was a slight burning sensation after application.[21] For solitary nodules, clindamycin lotion is an effective, safe and low-cost option.

2.2 Resorcinol cream

In our center resorcinol cream is commonly used. It has a peeling effect on the skin, due to its keratolytic properties at higher concentrations. It is hypothesized that it targets the follicular keratin plug, which is considered be a primary event in the pathogenesis of HS.[13,14,22] In addition, it also has an antiseptic effect. The effectiveness of resorcinol 10-15% has been described in a small study of twelve patients. After daily application, patients reported a decrease in pain and a reduction of the number of days the nodules and abscesses persisted.[23] In our clinical experience, resorcinol effectively prevents new inflammatory lesions by reducing follicular occlusion and it also helps to resolve active nodules faster. However, patients should be warned that resorcinol should be applied to limited skin areas to prevent systemic exposure due to absorption, and that it can have a discoloring effect on their skin and cloths. In addition, due to insufficient data, the use of resorcinol should be avoided during pregnancy.[22,23]

2.3 Other topical agents

Topical antiseptics, such as iodine scrubs or chlorhexidine, are widely used for HS.[20] They can be effective by preventing secondary bacterial infection of lesions. However, their efficacy in HS has never properly been investigated.

Azelaic acid is registered for mild acne. In vitro it has been shown to have antifungal and bacteriostatic properties, and to inhibit keratinocyte proliferation.[22,24] It is suggested that azelaic acid can have preventive properties in HS; however, this is based on clinical experience and no studies are available on its use in HS.[22] Nothing is known about the efficacy or usefulness in HS of topical agents such as salicylic acid, tretinoin, adapalene and benzoyl peroxide, which form the basis of treatment for acne vulgaris.

3. SYSTEMIC ANTIBIOTICS

Even though bacterial infections are not primarily involved in the early phase of the pathogenesis of HS, antibiotics are the treatment of first choice.[3] Cultures of HS lesions are often sterile or show common skin flora.[3,25,26] Most commonly found bacteria are coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, and strains of the intestinal flora such as *Proteus mirabilis*, *Enterococcus faecalis*, or *Escherichia coli*.[26–31] *S. aureus* is mostly cultured from chronic suppurative lesions, suggesting that it is not pathogenic in HS, but mostly a superinfection of already existing lesions.[27,30] CoNS are more often found in deep lesions. In addition, it has recently been shown that *Staphylococcus lugdunesis* was often found in Hurley stage I lesions, whereas in Hurley stage II or III more often a mixed group of anaerobic flora can be found, including strict anaerobes, anaerobic actinomycetes, and streptococci of the milleri group.[32] However, antibiotics are also thought to be effective because of their anti-inflammatory properties, and in addition by treating or preventing superinfections. In mild cases long-term antibiotics can lead to total remission (Table III). However, when fistulas, scars or fibrosis are pres-

Table III. An overview of articles published on systemic antibiotic for hidradenitis suppurativa

	n[a]	Dose and duration	Outcome
Tetracyclines			
Jemec and Wendelboe[37]	24	Tetracycline 500 mg bd, 3 months	Reduction in physicians' and patients' overall evaluation, soreness, and abscesses. No data on number of responders. No difference in results compared with clindamycin 1% lotion
Clindamycin and rifampicin			
Mendonça and Griffiths[46]	14	Clindamycin 300 mg bd, rifampicin 300 mg bd, 10 weeks	Eight showed complete remission, two switched from clindamycin to minocycline and four stopped because of side effects
Gener *et al.*[47]	70[b]	Clindamycin 300 mg bd, rifampicin 600 mg qd, 10 weeks	Eight showed complete response, 51 partial response and, three no response or worsening. Eight stopped because of side effects
Van der Zee *et al.*[48]	34	Different dose schemes and treatment durations	Sixteen showed complete remission, twelve partial remission, and no response in six patients
Bettoli *et al.*[49]	23	Clindamycin 600 mg qd, rifampicin 600 mg qd, 10 weeks	Seventeen showed response (reduction of 25% in Sartorius score). No response in three patients. Three stopped because of side effects or personal reasons
Rifampicin, moxifloxacin and metronidazole			
Join-Lambert *et al.*[54]	28	Rifampicin 10 mg/kg qd, moxifloxacin 400 mg qd, metronidazole 500 mg tid, minimum 6 weeks	Sixteen showed complete remission, and twelve partial remission

n - number of patients treated; qd - once daily; bd - twice per day; tid - three times per day

[a] Number of patients treated with systemic antibiotics with their treatment outcome

[b] 116 patients were treated, but no data available on the effectiveness of 46 patients.

ent, antibiotics are rarely curative, but they can reduce the amount of inflammation and improve conditions for surgery.

3.1 Tetracyclines

Antibiotics from the tetracycline group are the first-line systemic treatment for HS.[20,29,33] Tetracyclines are broad-spectrum antibiotics and act by inhibition of bacterial protein synthesis through reversible binding to the 30S ribosomal subunit.[34] In addition, tetracyclines have multiple nonantibiotic properties. They act in an anti-inflammatory fashion by suppressing chemotaxis and neutrophil migration, inhibiting the expression of nitric oxide synthase, downregulating pro-inflammatory cytokines such as TNF-α and IL-1β, and upregulating the anti-inflammatory cytokine IL-10.[34–36] Furthermore, they can inhibit angiogenesis,[35] which is a common process in HS inflammation.

Because of these anti-inflammatory properties and a mild side effect profile, tetracyclines are useful for long-term treatment and stabilization of HS.[29,33] However, they are less effective in treating or preventing exacerbations of HS. Matusiak *et al.* cultured the bacteria isolated from HS patients and found that 64% of the isolated strains were resistant for tetracyclines.[29] In addition, in a randomized double blind controlled trial, topical clindamycin 1% lotion was shown to be as effective as systemic tetracycline 500 mg twice daily in terms of number of nodules, abscesses and patients pain score.[37] Although no studies are available on the effectiveness of doxycycline or minocycline in HS, we believe that they can be very effective in mild HS when given for several months.

Common side effects of tetracyclines are photosensitivity, gastrointestinal complaints, and irreversible dental staining in children.[36,38] Tetracyclines should not be taken together with iron supplements, antacids or milk, because together they can form insoluble complexes in the intestine, and reduce their absorption. In addition, the use of tetracyclines during pregnancy is contraindicated because of the risk of intrauterine dental staining and hepatic necrosis in pregnant women.[39]

3.2 Clindamycin and rifampicin combination therapy

Most studies on antibiotics in HS have been published on the combination therapy of clindamycin and rifampicin. Clindamycin is produced by substituting chlorine to the hydroxyl group of lincomycin, an antibiotic isolated from a strain of *Streptomyces lincolnesis* in the early 1960s.[40] Clindamycin is a broad-spectrum antibiotic, and is effective against Gram-positive bacteria and strains of *S. aureus*, with the exception of *Streptococcus faecalis*. However, most aerobic Gram-negative bacteria are resistant to clindamycin.[40] Clindamycin binds to the 50S ribosomal subunit leading to inhibition of the bacterial protein synthesis. Besides its bacteriostatic effects, clindamycin has marked immune-enhancing properties. It enhances chemotaxis and phagocytosis, and increases TNF and IL-6 release.[41,42]

Rifampicin is a chemically modified version of rifamycin, a natural metabolite of *Nocardia mediterranei*, and is active against Gram-positive cocci (including *S. aureus*), Gram-negative cocci and bacilli, and most anaerobes. Its bactericidal action is by inhibition of bacterial DNA-dependent RNA polymerase, and is effective at extremely low concentrations and penetrates well into many body tissues.[43] Rifampicin also has mild immunosuppressive properties, which is not unexpected since it is structurally related to the clear immunosuppressive macrolides such as tacrolimus and rapamycin. It suppresses T cell function and in vitro it was shown to reduce lymphocyte transformation.[44] In vitro, rifampicin has also been shown to inhibit IL-1β and TNF-α secretion, whereas IL-6 and IL-10 secretion was significantly increased in rifampicin-treated mononuclear cells.[45]

For HS the most common regimen is clindamycin 300 mg twice daily, and rifampicin 600 mg once daily or 300 mg twice daily, for a period of ten weeks. To date, four studies have been published in which a total 187 patients were treated.[46–49] However, since in these studies different doses and different outcome variables were used to assess efficacy (Table III), it is difficult to compare or group these studies. In three retrospective studies, 164 patients were treated, of whom 88 patients completed a ten-week course of clindamycin 300 mg twice daily, and rifampicin 600 mg once daily or 300 mg twice daily.[46–48] Twenty-one patients could not complete the treatment period because of side effects, mostly diarrhea and nausea. No data were available for 55 patients regarding the efficacy after ten-weeks, or different dosage regimens were used. Of the 88 patients, 25 had a complete remission (28.4%) and another 57 showed a partial response (64.8%). In only six patients was the treatment either not effective or worsening was observed (6.8%). However, relapse rates of up to 61.5% have been reported after discontinuation of the therapy.[46–48] In the only prospective study available to date, 20 of 23 patients completed the ten-week treatment course, and of these 17 had a reduction of 25% in the Sartorius score. One patient stopped prematurely because of gastrointestinal side effects.[49]

It has been suggested that clindamycin and rifampicin have a synergistic bactericidal effect on *S. aureus* in vivo.[50] However, some studies have shown that the serum concentration of clindamycin is dramatically reduced, even up to 82% of the peak concentration, when given together with rifampicin.[51–53] Rifampicin is a potent inducer of cytochrome P450, whereas clindamycin is metabolized through a member of the cytochrome P450 system, namely CYP3A4. This might explain the low serum levels of clindamycin. In addition, when both are taken orally, rifampicin may reduce the hepatic first-pass effect of clindamycin, further reducing the bioavailability of clindamycin.[51]

Most common side effects of clindamycin as well as of rifampicin are gastrointestinal complaints, such as nausea, vomiting, and diarrhea.[40,44] In addition rifampicin can cause a red/orange discoloration to urine, sputum and tears, and can permanently discolor soft contact lenses.[44] Clindamycin is considered relatively safe for use during pregnancies,

since it is unlikely that children of women treated with clindamycin during pregnancy have a high risk of congenital anomalies.[39] However, for rifampicin insufficient data are available on use during pregnancy and therefore its use should be avoided during pregnancy.[39] Because rifampicin interferes with the metabolism of oral contraceptives, female patients should use extra birth control measures.[44]

3.3 Rifampicin, moxifloxacin and metronidazole triple therapy

For severe or therapy-resistant patients, the combination of rifampicin, moxifloxacin and metronidazole is an alternative therapeutic option.[54] Metronidazole was originally intended as an antiprotozoal agent that later proved very effective for Gram-negative anaerobic bacteria. In bacteria, it forms a redox intermediate metabolite causing DNA strand breakage, repair inhibition and ultimately disrupted transcription and cell death.[55] In addition, it has immunosuppressive properties. Metronidazole can decrease the level of IL-1β, IL-6, IL-8, IL-12, interferon (INF)-γ and TNF-α. It also has anti-inflammatory effects by blocking the migration of leukocytes from blood into the tissues.[56] Moxifloxacin is an extended-spectrum fluoroquinolone that inhibits bacterial DNA topoisomerases, influencing the replication, transcription, repair, and recombination of the bacterial DNA.[57] Moxifloxacin is a broad-spectrum antibiotic, and is effective against Gram-positive, Gram-negative and atypical respiratory pathogens. It also has shown to be effective against *S. aureus* and *S. pyogenes*. Furthermore, moxifloxacin has immunomodulatory properties; it inhibits the secretion of IL-1α and TNF-α by monocytes.[58] Moxifloxacin is not metabolized through the cytochrome P450, therefore its availability is not affected when taken together with rifampicin.

In a retrospective study by Lamber *et al.,* 28 HS patients were treated with the combination of rifampicin (10 mg/kg once daily), moxifloxacin (400 mg once daily) and metronidazole (500 mg three times daily). Sixteen patients in this study showed complete remission and another twelve patients showed a partial response.[54] To avoid neurological complaints, the metronidazole was stopped after six weeks, but reintroduced in four patients because of recurrence.[54] Over the past few years we have treated multiple HS patients with the above "triple therapy" with good results as long as the patients are taking the drugs.

The most common side effects of metronidazole are nausea, headache, and metallic taste. A serious but rare adverse effect of metronidazole is central or peripheral nervous system toxicity. In a recent review, Cação *et al*. reported on 84 cases of metronidazole-induced neurotoxicity.[59] In most cases (90.5%) the central nervous system (CNS) was involved, mostly causing cerebellar ataxia, encephalopathy, or seizures. In addition, polyneuropathy was reported in 26 cases. After discontinuation of the metronidazole, the CNS toxicity resolved in 92%, whereas 37% of the patients with polyneuropathy had complete resolution.[59] Patients with longer treatment duration or higher doses did

not seem to be at a higher risk of developing CNS toxicity.[60] It is important to inform patients to stop or minimize alcohol intake during treatment with metronidazole since this can lead to disulfiram-like reactions.[55] Most frequent side effects of moxifloxacin are nausea, diarrhea, and dizziness. In addition, it can cause QT_c-interval prolongation, therefore combination with class IA or class III antiarrhythmic drugs should be avoided.[57] The bioavailability of moxifloxacin is substantially reduced when taken together with antacids, sucralfate, or iron preparations.

All three antibiotics are contraindicated during pregnancy or breast-feeding. Female patients should use extra contraceptive measures because of the interaction of rifampicin with oral contraceptives.

4. BIOLOGICS

Since the early 2000s biologics are an upcoming treatment for HS. The efficacy of infliximab, a TNF-α inhibitor, was first described in HS patients with concomitant Crohn's disease (CD).[61,62] The first case was a 30-year-old female CD patient who developed perianal abscesses, later followed by inflammatory nodules in both axillae. Antibiotic therapies had only temporary effect. After one dose of infliximab all here lesions significantly improved, and after the second dose the patient stayed in remission for up to six months.[61] Shortly after, Katsanos *et al.* reported on a 39-year-old male CD patient who presented with bilateral fistulizing axillary HS. He was started on infliximab and after one year all of his fistulas dried up and closed.[62] In the following years, multiple case studies followed on the use of TNF-α inhibitors in HS. Other biologics were also given, such as adalimumab, etanercept, and anakinra. Recently the results of the first large randomized controlled multicenter trial on the use of adalimumab in HS patients has been published.[12] Even though biologics are seldom curative in HS, they can suppress the symptoms and can often be given for a prolonged period, making them a good treatment option for chronic HS. The negative aspects of biologics are the costs and that reimbursement is not covered by all insurance companies.[63]

Overall, anti-TNF-α biologics are well tolerated, and patients can be treated for prolonged periods.[12,64,65] The most common side effects are injection-site skin reactions or infusion reactions. Mostly they are a mild and transient local erythema, nodules, urticarial plaque, or pruritus. Patients on infliximab may develop hypersensitivity reactions such as generalized urticaria up to anaphylactic shock. Patients treated with adalimumab and infliximab, have a higher frequency of upper respiratory tract infections, rhinitis, bronchitis, and urinary tract infections.[12,66,67] Since TNF-α plays an essential role in the host immune response against tuberculosis (TB), it is known that TNF-α inhibitors can increase the risk of TB. Therefore, screening of all patients for latent TB before therapy is

mandatory. In addition, the presence of heart failure, hepatitis B infection and malignancies should be ruled out before therapy is started.[65,66] Since biologics might have an effect on the immune response in neonates, it is contraindicated during pregnancy and women should use adequate contraceptives for up to at least five half-lives after the last dose. They are also contraindicated during lactation, since biologics are secreted in breast milk.[3,65,66]

4.1 Infliximab

Infliximab is a chimeric monoclonal antibody consisting of the human IgG1 still containing a murine fragment of the antigen-biding (Fab) portion specific for TNF-α. It binds to the soluble and transmembrane forms of TNF-α, inhibiting TNF-α from binding to its receptors.[68] Multiple studies have reported on the efficacy of infliximab in patients with HS.[69–71] Mostly the same dose is given as in psoriasis, with 5 mg/kg infliximab at week 0, 2 and 6, and continued every 8 weeks thereafter.[3,72] Even though an improvement is often reported in the inflammatory lesions during infliximab therapy, recurrence is high also during therapy. Up to 50% develops new lesions after a treatment period of 37 weeks.[69–71] Moriatry *et al.* suggested that an eight-week interval is too long for HS patients and that a four-week interval is more effective,[71] because most patients report a gradual increase in inflammatory lesions around six weeks after infusion. In our experience, a six-week interval maintenance scheme works well in most HS patients. Shorter intervals for infliximab infusions are not recommended because they generally lead to more side effects and because of the cost aspects. Unfortunately, no trials have been done comparing different interval schemes of infliximab in patients with HS.

4.2 Adalimumab

Adalimumab is a fully human recombinant IgG1 monoclonal antibody against TNF-α. It binds soluble TNF-α and thereby prevents its interaction with TNFR1- and TNFR2-type cell receptors.[66] In addition, it changes levels of adhesion molecules responsible for leucocyte migration, and reduces serum concentrations of C-reactive protein, erythrocyte sedimentation rate, and IL-6.[66]

The first reports of the use of adalimumab in HS patients dates from 2006.[73,74] Initially it showed efficacy in an African American male with concomitant seronegative arthritis,[73] and later in a Caucasian male with concomitant inflammatory bowel disease.[74] Over the years multiple studies followed, reporting different clinical outcomes. Two prospective studies using a dose of 40 mg every other week showed initial improvement.[75,76] However, after twelve weeks of treatment no difference could be observed compared with baseline or with placebo. Nonetheless, these studies report on high recurrence rates after discontinuation.[75,76] It has been suggested that a weekly dose is more effective.[3] In a retrospective study Blanco *et al.* initially started with 40 mg every other week, but in

five of the six patients the dose had to be increased to 40 mg every week to prevent relapse.[64] In a large prospective randomized placebo-controlled trial, 40 mg adalimumab weekly was more effective than 40 mg every other week or placebo after 16 weeks of treatment.[12] However, of the weekly patients, only 18% achieved the clinical end-point (clear, moderate to mild response with a decrease of at least two grades). This response rate dropped further when at 16 weeks the dose was decreased to 40 mg every other week. Therefore, a high-dose regimen seems to be needed to suppress HS.[12]

4.2.1. Infliximab versus adalimumab

Only one retrospective study compared the effectiveness of infliximab with adalimumab.[77] Ten patients were treated for eight weeks with three courses of infliximab 5 mg/kg, whereas in the other group, ten patients were treated for a year with adalimumab 40 mg every other week. After one year the three courses of infliximab seemed more effective than continuous adalimumab.[77] However, it was not mentioned whether infliximab patients received other treatments during the follow-up period. In addition, as set out above, an every-other-week dosing regimen seems to be insufficient for HS.

4.3 Etanercept

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 TNF receptor, and the constant portion of IgG1. Etanercept binds and neutralizes the soluble TNF, transmembrane TNF, and lymphotoxin. In addition, it can alter dendritic-cell, T cell and neutrophil emigration.[65]

The first prospective open-label study of etanercept in HS showed promising results. Patients were treated with 50 mg etanercept subcutaneous every week. After twelve weeks six out of ten patients showed a decrease of more than 50% in disease activity. This effect remained in the twelve-week follow-up period.[78] However, in a later open-label and in a placebo-controlled studies, these results could not be reproduced.[79,80] In the open-label study 15 patients were treated with 50 mg weekly. Only ten completed the twelve-week treatment period, of whom three reached the primary end-point, a 50% reduction in the Physicians Global Assessment (PGA) score.[79] In the placebo-controlled trial, ten patients were treated with etanercept 50 mg twice weekly and ten received placebo. After twelve weeks of treatment, there was no difference in PGA, patients' global assessment, or DLQI between etanercept and placebo. In addition, in the following twelve-weeks open-label phase, no improvement was observed.[80] Therefore, etanercept is not a first choice biologic in HS.

4.4 Other biological treatments

4.4.1. Ustekinumab

Ustekinumab is a human monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23, preventing them from binding to their receptor.[81] To date, eight HS patients have been treated with 45 mg ustekinumab subcutaneously, mostly at week 0, 4 and 12, followed by every three months. Four patients showed a complete remission of their HS, three patients had a partial response, and one patient did not respond to ustekinumab treatment.[82–85] During the 23rd European Academy of Dermatology and Venereology (EADV) congress in 2014 in Amsterdam, Blok *et al.* presented the results of the first prospective open-label study of ustekinumab in HS patients.[86] Seventeen patients were treated with 45-90 mg, administered at weeks 0, 4, 16 and 28. Twelve patients completed the treatment protocol. A reduction of ≥50% in the modified Sartorius score was achieved by six patients (35%) at week 40, and another eight (47%) showed a moderate response (reduction of 25-50% in the modified Sartorius score). Five patients dropped out because of lack of efficacy, side effects, or psychological problems.[86,87]

4.4.2. Anakinra

Anakinra is a recombinant human IL-1 receptor antagonist that blocks the inflammatory effects of IL-1.[88] In HS elevated levels of IL-1 have been demonstrated in lesional and perilesional skin.[17] To date, ten patients have been treated with anakinra with mixed results.[89–93] In seven patients anakinra showed clear improvement of the HS lesions,[89,90,93] whereas in the other three patients with severe HS, anakinra was ineffective.[91,92] We await the results of a prospective, placebo-controlled trial with great interest to see the position of anakinra as a treatment option for HS.

5. OTHER ANTI-INFLAMMATORY DRUGS

5.1 Dapsone

Dapsone is an aniline derivate from the sulfone group.[94] It has not only antimicrobial and antiprotozoal properties, but it also has anti-inflammatory properties similar to those of nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, it can suppress the levels of IL-8 and TNF-α.[94] To date, two retrospective studies have been published on the use of dapsone for HS. Kaur and Lewis reviewed five cases of refractory HS treated with 50-150 mg of dapsone per day. All five patients showed improvement after four to twelve weeks of treatment.[95] In a later series of 24 patients treated with 50-200 mg per day, nine patients showed slight to clinically significant improvement, whereas the other 15 did not respond to dapsone therapy.[96]

5.2 Fumaric acid ester derivatives (fumarates)

In Europe, fumarates are a common treatment for psoriasis because of their immunomodulatory and anti-inflammatory effects.[72] Among other multiple effects, they impair IL-12 and IL-23 production by dendritic cells and macrophages.[97] Our department has recently reported on the use of fumarates in HS.[98] Seven patients with moderate to severe HS were treated with fumarates in a progressive dosage scheme up to 720 mg a day. After 20 weeks of treatment only one patient showed clear improvement, but two others reported reduced inflammation with lesions that resolved faster. Therefore, treatment was continued and after 28 weeks all three showed slight to clear improvement. Two patients continued up to one year with clear improvement of their HS. However, four patients stopped after 20 weeks due to lack of efficacy and one patient stopped after 28 weeks because of persistent diarrhea.[98]

5.3 Cyclosporine

Cyclosporine is a calcineurin inhibitor and a potent immunosuppressive drug.[99] It suppresses IL-2 production, and in the epidermis and dermis cyclosporine causes a depletion of lymphocytes and macrophages. It also inhibits the activation of T cells, natural killer cells and antigen-presenting cells. In addition, cyclosporine can inhibit keratinocyte hyperproliferation.[99] To date, only a few cases have been reported on the use of cyclosporine in HS. Four patients with recalcitrant HS showed significant improvement after treatment with 3-5 mg/kg cyclosporine per day.[100–102] However, randomized controlled trials and larger case series are lacking on the effectiveness of cyclosporine in HS.

5.4 Systemic and intralesional steroids

Because of their anti-inflammatory and immunosuppressive properties, systemic steroids have always been widely used in dermatology. They are often mentioned as a treatment option for HS,[3,103,104] and in a survey among physicians interested in HS from the UK, a quarter responded that prednisolone was one of their top ten treatment choices for HS.[20] A short-term treatment of 0.5-0.7 mg/kg can be used to control acute flares.[3,103] However, reports on the use of oral steroids in HS date from more than 25 years ago, and no recent studies are available.

The use of intralesional corticosteroids is mostly based on clinical experience, but they are often used for solitary inflammatory nodules.[3,20] Intralesional injection of 5-10 mg/ml, can cause a rapid reduction of the nodules and is in our opinion a good option for single recalcitrant inflammatory nodules.[3,22]

5.5 Azathioprine

Azathioprine is a purine antagonist with immunosuppressive, immunomodulating and anti-inflammatory properties. In a small retrospective study of nine HS patients, azathio-

prine was ineffective in five patients, and the other three showed only slight improvement.[105] However, the therapeutic effects of azathioprine are normally reached after two to three months, and six patients were treated for six weeks or fewer due to side effects. In addition, the therapeutic range of azathioprine is 1-3 mg/kg, but in five patients the dose remained below 1 mg/kg. Therefore, it is possible that azathioprine was ineffective due to a too short treatment duration and too low dosing.[105]

5.6 Colchicine

The anti-inflammatory drug colchicine accumulates in neutrophils, inhibits neutrophil expression of cell adhesion molecules, and decreases neutrophil degranulation, chemotaxis and phagocytosis.[106,107] In a small case series of eight HS patients, colchicine did not show any clinical improvement. Six patients dropped out before the end of the study because of lack of efficacy. Of the two patients who completed the four month period, only one showed slight improvement.[107]

5.7 Methotrexate

Methotrexate is an anti-inflammatory and immunosuppressive drug that is often used for treating psoriasis, psoriatic arthritis, or rheumatoid arthritis.[108] In a report on three HS patients, a dose of 12.5-15 mg per week did not have any effect on the existing lesions nor did it reduce the number of flare-ups.[109]

6. RETIONOIDS

6.1 Isotretinoin

The vitamin A derivate, isotretinoin is naturally present in small amounts in the blood and tissue. It has an antiproliferative effect on sebocytes, it inhibits cell differentiation and sebum secretion, and reduces the size of the sebaceous glands. In addition, it has anti-inflammatory, immunomodulatory, and antineoplastic properties.[110] The use of isotretinoin for HS comes from the former belief that HS is associated with acne vulgaris. However, in HS the sebaceous glands are not primarily affected and there is no evident seborrhea.[111] Even though multiple studies reported the lack of efficacy of isotretinoin in HS,[112–114] it is still often prescribed for this condition.[20] Blok *et al.* reviewed seven papers in which isotretinoin were used for HS. In total, 174 patients were treated, of whom only 32 reported significant improvement (18%), 30 moderate improvement (17%), and in 112 patients no response was observed (64%).[115] Therefore, isotretinoin should not be prescribed for standard HS, and should only be considered if patients have concomitant acne vulgaris. Isotretinoin is highly teratogenic, therefore female patients should use

adequate contraceptives, up to six months after therapy, and pregnancy test should routinely be performed.

6.2 Acitretin

Originally etretinate was the first retinoid registered for psoriasis, but its use was limited because of its unfavorable pharmacokinetic profile with a very long elimination time and teratogenic effects. It was later replaced by acitretin, which was derived from etretinate, but had a shorter half-life.[116] Acitretin has anti-inflammatory properties and modulates the cellular differentiation, proliferation, and cornification of the epidermis.[116,117] Most importantly it influences the process of hyperkeratosis of the infundibular follicular epithelium, which is primary involved in the pathogenesis of HS.[13,14,117] In a retrospective study of Boer and Nazary, all twelve treated patients showed a positive response to 0.25-0.88 mg/kg acitretin for a period of nine to twelve months. Nine out of twelve patients achieved a marked or complete remission, whereas the other three had a mild to moderate response. All patients reported cheilitis as a side effect.[117] In a recent prospective study, 17 patients were treated with 0.5-0.6 mg/kg.[118] Nine patients completed the nine-month treatment period, of whom eight achieved the clinical endpoint, a reduction of 50% in the HS Severity Index (HSSI). Drop-out was mostly because of ineffectiveness or side effects.[118] Like isotretinoin, acitretin is teratogenic, and major human fetal abnormalities are associated with retinoid use during pregnancy. Female patients should use adequate contraceptives up to two years after discontinuation, since, especially in the presence of ethanol, acitretin converts to etretinate, which takes two years to be completely eliminated from the fatty tissue.[116]

6.3 Alitretinoin

Alitretinoin is a vitamin A derivative and is registered for severe chronic hand eczema. Recently the first study on the use of alitretinoin in HS has been published.[119] Fourteen patients were treated with 10 mg alitretinoin daily for a period of 24 weeks. Six patients showed significant improvement, with a reduction of 50% in the Sartorius score. Another five patients reported improvement; however, this was less than a 50% reduction in the Sartorius score. Only three patients did not respond.[119] Alitretinoin is very similar to acitretin, accept for its much shorter half-life, making it a better treatment option for female patients. Contraceptives have to be used up to one month after treatment discontinuation.

7. OTHER MEDICAL TREATMENTS

7.1 Zinc

Zinc plays a role in the innate and adaptive immunity. It is believed that zinc can alter the differentiation and function of T cells, and that it activates natural killer cells and the phagocytic function of granulocytes. In addition, it leads to an increased production of IL-6, IL-1β and TNF-α.[120,121] In a pilot-study, 22 patients started with 90 mg of zinc and the dose was reduced with 15 mg every two months. Eight patients showed complete remission, and partial remission was achieved in the other 14 patients. Relapse occurred when doses lower than 30 to 60 mg were given. Gastrointestinal discomfort was the most common side effect and was reported by four patients.[121]

7.2 Metformin

Metformin is an insulin sensitizer and is a first-line treatment option for patients with diabetes type II. Metformin also has anti-oxidative and anti-androgenic properties and has been shown to inhibit human immortalized keratinocytes in vitro.[122,123] Metformin was initially reported to have an effect on HS, after a woman reported worsening of her HS after metformin was stopped.[124] In prospective study, 25 HS patients were treated with a progressive dose scheme up to a maximum of 500 mg three times a day. Eighteen patients showed clinical improvement, with seven having a reduction of more than 50% in the Sartorius score. The other seven patients were unresponsive to the treatment. Only minor gastrointestinal side effects were reported at the beginning of the treatment.[123]

8. HORMONAL TREATMENT

The role of sex hormones in the pathogenesis of HS is still under debate. The clinical course of HS would suggest a role of sex hormones, due to the post-pubertal onset, female predisposition, reports of peri-menstrual flares, and improvement during pregnancies.[25,104,125] However, no difference was found in androgen levels between HS patients and body mass index (BMI)-matched controls.[126]

8.1 Finasteride

Finasteride is a 5α-reductase inhibitor that inhibits the conversion of testosterone to dihydrotestosterone.[127] It was originally approved for treatment of benign prostatic hypertrophy and later for androgenetic alopecia in men. To date, the use of finasteride has been reported in twelve HS patients, eight adults and four children. Seven adult patients showed a good response on 5 mg finasteride daily after a treatment period of two to twelve weeks.[128,129] Two patients showed recurrence, one month after discontinu-

ation. The four female children were treated with finasteride 1.25-10 mg daily with good effect. However, all received additional treatment with oral contraceptives, antibiotics, or surgery.[129,130]

Side effects of finasteride in men are decreased libido and gynecomastia. Finasteride should not be used during pregnancy due to feminization of the male fetus.[127]

8.2 Cyproterone acetate

In 1986, Sawers *et al.* reported on the effectiveness of the antiandrogen cyproterone acetate combined with estrogen in four female HS patients.[131] However, a double-blind controlled trial comparing ethinyloestradiol 50µg/cyproterone 50 mg with ethinyloestradiol 50µg/norgestrel 500µg showed no difference between the two groups. However, of the 18 patients from both groups that completed the trial, twelve showed a good response, suggesting that both hormonal therapies can be effective in HS.[132] However, larger, well powered studies on the use of hormonal therapy in HS are lacking.

9. PAIN TREATMENT

Pain management is a crucial part of the treatment of HS. However, no studies are available on the use of analgesics in HS. Only two reviews have been published on the pain management in HS patients.[133,134] Even though these are comprehensive reviews on a broad spectrum of analgesics, its use in HS is mostly based on clinical experience.[133,134] First of all it is recommended that a visual analogue scale (VAS) is used to assess the pain level of the patients, and this can also be a guide to evaluate if the prescribed analgesics are sufficient. For moderate constant pain, oral acetaminophen (paracetamol) 1000 mg four times per day is often the first step in pain treatment. In general, acetaminophen is well tolerated; however, excessive doses can lead to liver toxicity.[133,134] When acetaminophen does not sufficiently reduce the level of pain, or when the patient complains of sporadic acute pain, NSAIDs are indicated. The dose depends on which NSAID is chosen, and standard regimens are recommended.[3] There is no evidence that one NSAID is superior to another.[133,134] Long-term use of NSAIDs can increase the risk of gastric ulcers, therefore proton pump inhibitors are recommended when patients use NSAIDs on a frequent basis. When patients have high levels of chronic pain, opiates are indicated.[3] Codeine is the first option of this drug class, due to its lower risk on addiction. When higher levels of pain medication are needed, referral to a pain team is recommended.[133]

10. LIFESTYLE CHANGES

Smoking and obesity are strong risk factors for HS. Most HS patients are active smokers (66-71%) or ex-smokers (8-15%), and 51-82% of patients are overweight or obese, with a BMI > 25kg/m^2.[135–138] Disease severity is positively correlated with BMI,[135–137] and case reports have demonstrated remission of HS after extensive weight loss.[139,140] In one study patients were asked after bariatric surgery if they had suffered from HS before the operation and if the symptoms had changed after the operation. After a decrease in BMI of 15%, half of the patients stated they were free of inflammation and another 20% reported to have fewer symptoms.[141] Since HS is also associated with metabolic syndrome,[142] patients with HS should be strongly advised to reduce weight.

The exact effect of smoking cessation on HS is still unclear. However, it is thought that smoking can trigger the onset of HS, and heavy smokers tend to have a more severe disease than non- or mild smokers.[135–137] In a study on the clinical course, patients were asked 22 years after the diagnosis was made, if they still suffered from HS. Nonsmokers and ex-smokers were more often disease-free than active smokers, indicating that smoking cessation contributes to disease remission. This is supported by a case report of two patients who became free of symptoms after they quitted smoking. However, mostly cessation does not give instant improvement of the disease,[143] often leading to disappointment in the patients and causing them to restart smoking. Patients should be well educated that they should not expect instant relief after cessation but that it helps towards improvement or even remission over the years. We believe that active referral of patients with HS to their general practitioner or any other "Stop smoking" and/or "Weight loss" program is essential.

11. FUTURE OPTIONS

Recently, elevated levels of IL-17 and IL-23 have been found in lesional HS skin.[18,19] These findings point towards new treatment options. Biologics targeting IL-17 are secukinumab, ixekizumab and brodalumab. Secukinumab is a fully human IgG1 monoclonal antibody against IL-17A, whereas ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes IL-17A, and brodalumab a human IgG2 monoclonal antibody that blocks IL-17R, a receptor subunit shared by IL-17A, IL-17F, and IL17A/F heterodimer ligands.[144,145] It is also possible to target IL-23 alone, with tildrakizumab or guselkumab. Tildrakizumab is a humanized IgG1k monoclonal antibody against IL-23p19, whereas it does not bind to IL-12 or the p40 subunit, just like guselkumab which is a human IgG1 monoclonal antibody against IL-23p19.[144]

Another immunomodulating drug is apremilast. It is a selective inhibitor of phosphodiesterase 4, and has shown in vivo to inhibit the production of the pro-inflammatory cytokines (e.g. IL-2, IL-5, IL-12A, IL-13, IL-17 IL-23A, TNF-α, INF-α and INF-γ), and chemokines (e.g. CXCL9 and CXCL10).[146]

Even though, these therapeutic options have shown to be effective in psoriasis,[144–146] no studies are available on their use in HS.

12. CONCLUSION

Hidradenitis suppurativa is a chronic inflammatory skin disease. Over the years multiple treatment options for HS have been suggested; however, so far none has been curative for HS. In mild disease, clindamycin lotion or resorcinol cream can give long-term remission. When these are insufficient or in more severe HS, mostly tetracyclines are first-line systemic options. However, the combination of clindamycin with rifampicin is the best-documented antibiotic treatment for HS, and is often effective in moderate to severe HS. Although antibiotics can be effective in reducing the number of inflamed lesions, recurrence rate is high after discontinuation. A more long-term treatment option is possible using retinoids, especially acitretin; however, due to their teratogenicity, they are less useful for females in the reproductive age. When patients fail to respond to most common treatments, biologics (e.g. infliximab or adalimumab) are the next step. Multiple anti-inflammatory drugs have been suggested for HS, such as dapsone, fumarates or cyclosporine. However, their effectiveness in HS is based on small case series with varying results. Although not addressed in this review, surgical interventions are often needed to achieve remission, especially when sinus tracts or scaring are present. For every patient treatment should be chosen based on the clinical presentation of the HS and the preferences of the patient.

REFERENCES

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

2 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

3 Zouboulis CC, Desai N, Emtestam L, *et al.* European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; **29**: 619–644.

4 Deckers IE, van der Zee HH, Boer J, Prens EP. Correlation of early-onset hidradenitis suppurativa with stronger genetic susceptibility and more widespread involvement. *J Am Acad Dermatol* 2015; **72**: 485–488.

5 Bettoli V, Ricci M, Zauli S, Virgili A. Hidradenitis suppurativa–acne inversa: a relevant dermatosis in pediatric age. *Br J Dermatol* 2015; **173**: 1328–1330.

6 Cosmatos I, Matcho A, Weinstein R, *et al.* Analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States. *J Am Acad Dermatol* 2013; **68**: 412–419.

7 Jemec GBE, Heidenheim M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential precursor lesions. *J Am Acad Dermatol* 1996; **35**: 191–194.

8 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

9 Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. In: Dermatologic Surgery (Roenigh R, Roenigh H, eds). Marcel Dekker, *New York* 1989; 729–739.

10 Sartorius K, Lapins J, Emtestam L, Jemec GBE. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. *Br J Dermatol* 2003; **149**: 211–213.

11 Canoui-Poitrine F, Revuz JE, Wolkenstein P, *et al.* Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. *J Am Acad Dermatol* 2009; **61**: 51–57.

12 Kimball AB, Kerdel F, Adams D, *et al.* Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med* 2012; **157**: 846–855.

13 Yu CC, Cook MG. Hidradenitis suppurativa: a disease of follicular epithelium, rather than apocrine glands. *Br J Dermatol* 1990; **122**: 763–769.

14 Boer J, Weltevreden EF. Hidradenitis suppurativa or acne inversa. A clinicopathological study of early lesions. *Br J Dermatol* 1996; **135**: 721–725.

15 von Laffert M, Helmbold P, Wohlrab J, *et al.* Hidradenitis suppurativa (acne inversa): early inflammatory events at terminal follicles and at interfollicular epidermis. *Exp Dermatol* 2010; **19**: 533–537.

16 Von Laffert M, Stadie V, Wohlrab J, Marsch WC. Hidradenitis suppurativa/acne inversa: bilocated epithelial hyperplasia with very different sequelae. *Br J Dermatol* 2011; **164**: 367–371.

17 van der Zee HH, de Ruiter L, van den Broecke DG, *et al.* Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. *Br J Dermatol* 2011; **164**: 1292–1298.

18 Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011; **65**: 790–798.

19 Kelly G, Hughes R, Mc Garry T, *et al.* Dysregulated cytokine expression in lesional and non-lesional skin in Hidradenitis suppurativa. *Br J Dermatol* 2015; **173**: 1431–1439.

20 Ingram JR, McPhee M. Management of hidradenitis suppurativa: a UK survey of current practice. *Br J Dermatol* 2015; **173**: 1070–1072.

21 Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. *Int J Dermatol* 1983; **22**: 325–328.

22 Sartorius K, Boer J, Jemec GBE. Topical treatment. In: Hidradenitis Suppurativa (Jemec GBE, Revuz J, Leyden JJ, eds) Springer, 2006: 150–160.

23 Boer J, Jemec GBE. Resorcinol peels as a possible self-treatment of painful nodules in hidradenitis suppurativa. *Clin Exp Dermatol* 2010; **35**: 36–40.

24 Detmar M, Mayer-da-Silva A, Stadler R, Orfanos CE. Effects of azelaic acid on proliferation and ultrastructure of mouse keratinocytes in vitro. *J Invest Dermatol* 1989; **93**: 70–74.

25 Deckers IE, van der Zee HH, Prens EP. Epidemiology of Hidradenitis Suppurativa: Prevalence, Pathogenesis, and Factors Associated with the Development of HS. *Curr Dermatol Rep* 2014; **3**: 54–60.

26 Jemec GBE, Faber M, Gutschik E, Wendelboe P. The bacteriology of hidradenitis suppurativa. *Dermatology* 1996; **193**: 203–206.

27 Lapins J, Jarstrand C, Emtestam L. Coagulase-negative staphylococci are the most common bacteria found in cultures from the deep portions of hidradentis suppurativa lesions, as obtained by carbon dioxide laser surgery. *Br J Dermatol* 1999; **140**: 90–95.

28 Sartorius K, Killasli H, Oprica C, *et al.* Bacteriology of hidradenitis suppurativa exacerbations and deep tissue cultures obtained during carbon dioxide laser treatment. *Br J Dermatol* 2012; **166**: 879–883.

29 Matusiak Ł, Bieniek A, Szepietowski JC. Bacteriology of hidradenitis suppurativa - which antibiotics are the treatment of choice? *Acta Derm Venereol* 2014; **94**: 699–702.

30 Nikolakis G, Join-Lambert O, Karagiannidis I, *et al.* Bacteriology of hidradenitis suppurativa/acne inversa: A review. *J Am Acad Dermatol* 2015; **73**: S12–S18.

31 Ring HC, Riis Mikkelsen P, Miller IM, *et al.* The bacteriology of hidradenitis suppurativa: a systematic review. *Exp Dermatol* 2015; **24**: 727–731.

32 Guet-Revillet H, Coignard-Biehler H, Jais J-P, *et al.* Bacterial Pathogens Associated with Hidradenitis Suppurativa, France. *Emerg Infect Dis* 2014; **20**: 1990–1998.

33 Collier F, Smith RC, Morton CA. Diagnosis and management of hidradenitis suppurativa. *BMJ* 2013; **346**: f2121.

34 Pasquale TR, Tan JS. Nonantimicrobial effects of antibacterial agents. *Clin Infect Dis* 2005; **40**: 127–135.

35 Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006; **54**: 258–265.

36 Monk E, Shalita A, Siegel DM. Clinical applications of non-antimicrobial tetracyclines in dermatology. *Pharmacol Res* 2011; **63**: 130–145.

37 Jemec GBE, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. *J Am Acad Dermatol* 1998; **39**: 971–974.

38 Simonart T, Dramaix M, De Maertelaer V. Efficacy of tetracyclines in the treatment of acne vulgaris: a review. *Br J Dermatol* 2008; **158**: 208–216.

39 Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol* 2006; **107**: 1120–1138.

40 Leigh DA. Antibacterial activity and pharmacokinetics of clindamycin. *J Antimicrob Chemother* 1981; **7**: 3–9.

41 Van Vlem B, Vanholder R, De Paepe P, *et al.* Immunomodulating effects of antibiotics: literature review. *Infection* 1996; **24**: 275–291.

42 Tufano MA, Cipollaro de l'Ero G, Ianniello R, *et al.* Antimicrobial Agents Induce Monocytes to Release IL-1α, IL-6, and Tnf and Induce Lymphocytes to Release IL-4 and TNFτ. *Immunopharmacol Immunotoxicol* 1992; **14**: 769–782.

43 Sensi P. History of the development of rifampin. *Rev Infect Dis* 1983; **5**: S402–S406.

44 Tsankov N, Angelova I. Rifampin in dermatology. *Clin Dermatol* 2003; **21**: 50–55.

45 Ziglam HM, Daniels I, Finch RG. Immunomodulating activity of rifampicin. *J Chemother* 2004; **16**: 357–361.

46 Mendonça CO, Griffiths CEM. Clindamycin and rifampicin combination therapy for hidradenitis suppurativa. *Br J Dermatol* 2006; **154**: 977–978.

47 Gener G, Canoui-Poitrine F, Revuz JE, *et al.* Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. *Dermatology* 2009; **219**: 148–154.

48 van der Zee HH, Boer J, Prens EP, Jemec GBE. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. *Dermatology* 2009; **219**: 143–147.

49 Bettoli V, Zauli S, Borghi A, *et al.* Oral clindamycin and rifampicin in the treatment of hidradenitis suppurativa-acne inversa: a prospective study on 23 patients. *J Eur Acad Dermatol Venereol* 2014; **28**: 125–126.

50 Renneberg J, Karlsson E, Nilsson B, Walder M. Interactions of drugs acting against Staphylococcus aureus in vitro and in a mouse model. *J Infect* 1993; **26**: 265–277.

51 Join-Lambert O, Ribadeau-Dumas F, Jullien V, *et al.* Dramatic reduction of clindamycin plasma concentration in hidradenitis suppurativa patients treated with the rifampin-clindamycin combination. *Eur J Dermatol* 2014; **24**: 94–95.

52 Bernard A, Kermarrec G, Parize P, *et al.* Dramatic reduction of clindamycin serum concentration in staphylococcal osteoarticular infection patients treated with the oral clindamycin-rifampicin combination. *J Infect* 2015; **71**: 200–206.

53 Curis E, Pestre V, Jullien V, *et al.* Pharmacokinetic variability of clindamycin and influence of rifampicin on clindamycin concentration in patients with bone and joint infections. *Infection* 2015; **43**: 473–481.

54 Join-Lambert O, Coignard H, Jais J, *et al.* Efficacy of rifampin-moxifloxacin-metronidazole combination therapy in hidradenitis suppurativa. *Dermatology* 2011; **222**: 49–58.

55 Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999; **36**: 353–373.

56 Shakir L, Javeed A, Ashraf M, Riaz A. Metronidazole and the immune system. *Pharmazie* 2011; **66**: 393–398.

57 Muijsers RBR, Jarvis B. Moxifloxacin. *Drugs* 2002; **62**: 967–973.

58 Dalhoff A. Immunomodulatory activities of fluoroquinolones. *Infection* 2005; **33**: 55–70.

59 Cação G, Fontes S, Salgado M, *et al.* Metronidazole-induced central and peripheral nervous system toxicity. *Neurol Sci* 2015; **36**: 1737–1739.

60 Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. *Clin Neuropharmacol* 2011; **34**: 241–247.

61 Martínez F, Nos P, Benlloch S, Ponce J. Hidradenitis suppurativa and Crohn's disease: response to treatment with infliximab. *Inflamm Bowel Dis* 2001; **7**: 323–326.

62 Katsanos KH, Christodoulou DK, Tsianos E V. Axillary hidradenitis suppurativa successfully treated with infliximab in a Crohn's disease patient. *Am J Gastroenterol* 2002; **97**: 2155–2156.

63 Kirby JS, Miller JJ, Adams DR, Leslie D. Health Care Utilization Patterns and Costs for Patients With Hidradenitis Suppurativa. *JAMA Dermatol* 2014; **150**: 937–944.

64 Blanco R, Martínez-Taboada VM, Villa I, *et al.* Long-term successful adalimumab therapy in severe hidradenitis suppurativa. *Arch Dermatol* 2009; **145**: 580–584.

65 Kerensky TA, Gottlieb AB, Yaniv S, Au S. Etanercept: efficacy and safety for approved indications. *Expert Opin Drug Saf* 2012; **11**: 121–139.

66 Traczewski P, Rudnicka L. Adalimumab in dermatology. *Br J Clin Pharmacol* 2008; **66**: 618–625.

67 Mrowietz U, Reich K. Ten years of infliximab: Its role in dermatology. *Eur J Pharmacol* 2009; **623**: S10–S16.

68 Castelo-Soccio L, Van Voorhees AS. Long-term efficacy of biologics in dermatology. *Dermatol Ther* 2009; **22**: 22–33.

69 Grant A, Gonzalez T, Montgomery MO, *et al.* Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol* 2010; **62**: 205–217.

70 Paradela S, Rodríguez-Lojo R, Fernández-Torres R, *et al.* Long-term efficacy of infliximab in hidradenitis suppurativa. *J Dermatolog Treat* 2012; **23**: 278–283.

71 Moriarty B, Jiyad Z, Creamer D. Four-weekly infliximab in the treatment of severe hidradenitis suppurativa. *Br J Dermatol* 2014; **170**: 986–987.

72 Pathirana D, Ormerod AD, Saiag P, *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; **23**: 1–70.

73 Scheinfeld N. Treatment of coincident seronegative arthritis and hidradentis supprativa with adalimumab. *J Am Acad Dermatol* 2006; **55**: 163–164.

74 Moul DK, Korman NJ. Severe hidradenitis suppurativa treated with adalimumab. *Arch Dermatol* 2006; **142**: 1110–1112.

75 Miller I, Lynggaard CD, Lophaven S, *et al.* A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. *Br J Dermatol* 2011; **165**: 391–398.

76 Amano M, Grant A, Kerdel FA. A prospective open-label clinical trial of adalimumab for the treatment of hidradenitis suppurativa. *Int J Dermatol* 2010; **49**: 950–955.

77 van Rappard DC, Leenarts MFE, Meijerink-van't Oost L, Mekkes JR. Comparing treatment outcome of infliximab and adalimumab in patients with severe hidradenitis suppurativa. *J Dermatolog Treat* 2012; **23**: 284–289.

78 Giamarellos-Bourboulis EJ, Pelekanou E, Antonopoulou A, *et al.* An open-label phase II study of the safety and efficacy of etanercept for the therapy of hidradenitis suppurativa. *Br J Dermatol* 2008; **158**: 567–572.

79 Lee RA, Dommasch E, Treat J, *et al.* A prospective clinical trial of open-label etanercept for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol* 2009; **60**: 565–573.

80 Adams DR, Yankura JA, Fogelberg AC, Anderson BE. Treatment of hidradenitis suppurativa with etanercept injection. *Arch Dermatol* 2010; **146**: 501–504.

81 Sehgal VN, Pandhi D, Khurana A. Biologics in dermatology: An integrated review. *Indian J Dermatol* 2014; **59**: 425–441.

82 Gulliver WP, Jemec GBE, Baker KA. Experience with ustekinumab for the treatment of moderate to severe hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2012; **26**: 911–914.

83 Baerveldt EM, Kappen JH, Thio HB, *et al.* Successful long-term triple disease control by ustekinumab in a patient with Behçet's disease, psoriasis and hidradenitis suppurativa. *Ann Rheum Dis* 2013; **72**: 626–627.

84 Sharon VR, Garcia MS, Bagheri S, *et al.* Management of recalcitrant hidradenitis suppurativa with ustekinumab. *Acta Derm Venereol* 2012; **92**: 320–321.

85 Santos-Pérez MI, García-Rodicio S, del Olmo-Revuelto MA, Pozo-Román T. Ustekinumab for hidradenitis suppurativa: a case report. *Actas Dermosifiliogr* 2014; **105**: 720–722.

86 Blok JL, Li K, Brodmerkel C, *et al.* Ustekinumab in hidradenitis suppurativa: A clinical open label study with analyses of the protein expression profile in serum. FCO3.8. 23rd European Academy of Dermatology Congress, Amsterdam, Oct 8-12, 2014.

87 Blok JL, Li K, Brodmerkel C, *et al.* Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. *Br J Dermatol* 2015; **Epub ahead of print**.

88 Pazyar N, Feily A, Yaghoobi R. An overview of interleukin-1 receptor antagonist, anakinra, in the treatment of cutaneous diseases. *Curr Clin Pharmacol* 2012; **7**: 271–275.

89 Hsiao JL, Antaya RJ, Berger T, *et al.* Hidradenitis suppurativa and concomitant pyoderma gangrenosum: a case series and literature review. *Arch Dermatol* 2010; **146**: 1265–1270.

90 Zarchi K, Dufour DN, Jemec GBE. Successful Treatment of Severe Hidradenitis Suppurativa With Anakinra. *JAMA Dermatol* 2013; **149**: 1192–1194.

91 Van der Zee HH, Prens EP. Failure of anti-interleukin-1 therapy in severe hidradenitis suppurativa: A case report. *Dermatology* 2013; **226**: 97–100.

92 Menis D, Maroñas-Jiménez L, Delgado-Marquez AM, *et al.* Two cases of severe Hidradenitis Suppurativa with failure of anakinra therapy. *Br J Dermatol* 2015; **172**: 810–811.

93 Leslie K, Tripathi S, Nguyen T, *et al.* An open-label study of anakinra for the treatment of moderate to severe hidradenitis suppurativa. *J Am Acad Dermatol* 2014; **70**: 243–251.

94 Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res* 2014; **306**: 103–124.

95 Kaur MR, Lewis HM. Hidradenitis suppurativa treated with dapsone: a case series of five patients. *J Dermatolog Treat* 2006; **17**: 211–213.

96 Yazdanyar S, Boer J, Ingvarsson G, *et al.* Dapsone therapy for hidradenitis suppurativa: a series of 24 patients. *Dermatology* 2011; **222**: 342–346.

97 Ghoreschi K, Brück J, Kellerer C, *et al.* Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. *J Exp Med* 2011; **208**: 2291–2303.

98 Deckers IE, Zee HH, Balak DMW, Prens EP. Fumarates, a new treatment option for therapy-resistant hidradenitis suppurativa: a prospective open-label pilot study. *Br J Dermatol* 2015; **172**: 828–829.

99 Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol* 2010; **63**: 925–946.

100 Buckley DA, Rogers S. Cyclosporin-responsive hidradenitis suppurativa. *J R Soc Med* 1995; **88**: 289P – 290P.

101 Rose R, Goodfield M, Clark S. Treatment of recalcitrant hidradenitis suppurativa with oral cyclosporin. *Clin Exp Dermatol* 2006; **31**: 154–155.

102 Bianchi L, Hansel K, Stingeni L. Recalcitrant severe hidradenitis suppurativa successfully treated with cyclosporine A. *J Am Acad Dermatol* 2012; **67**: e278–e279.

103 Nybæk H, Jemec GBE. Immunosuppressive Therapy. In: Hidradenitis Suppurativa (Jemec GBE, Revuz J, Leyden JJ, eds) Springer, 2006: 136–140.

104 Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. *J Am Acad Dermatol* 2009; **60**: 539–561.

105 Nazary M, Prens EP, Boer J. Azathioprine Lacks Efficacy in Hidradenitis Suppurativa: A retrospective study of 9 patients. *Br J Dermatol* 2015; **Epub ahead of print**.

106 Cocco G, Chu DCC, Pandolfi S. Colchicine in clinical medicine. A guide for internists. *Eur J Intern Med* 2010; **21**: 503–508.

107 Van der Zee HH, Prens EP. The anti-inflammatory drug colchicine lacks efficacy in hidradenitis suppurativa. *Dermatology* 2011; **223**: 169–173.

108 Yélamos O, Puig L. Systemic methotrexate for the treatment of psoriasis. *Expert Rev Clin Immunol* 2015; **11**: 553–563.

109 Jemec GBE. Methotrexate is of limited value in the treatment of hidradenitis suppurativa. *Clin Exp Dermatol* 2002; **27**: 528–529.

110 Nickle SB, Peterson N, Peterson M. Updated Physician's Guide to the Off-label Uses of Oral Isotretinoin. *J Clin Aesthet Dermatol* 2014; **7**: 22–34.

111 Jemec GBE, Hansen U. Histology of hidradenitis suppurativa. *J Am Acad Dermatol* 1996; **34**: 994–999.

112 Norris JFB, Cunliffe WJ. Failure of treatment of familial widespread hidradenitis suppurativa with isotretinoin. *Clin Exp Dermatol* 1986; **11**: 579–583.

113 Boer J, van Gemert MJP. Long-term results of isotretinoin in the treatment of 68 patients with hidradenitis suppurativa. *J Am Acad Dermatol* 1999; **40**: 73–76.

114 Soria A, Canoui-Poitrine F, Wolkenstein P, *et al.* Absence of efficacy of oral isotretinoin in hidradenitis suppurativa: a retrospective study based on patients' outcome assessment. *Dermatology* 2009; **218**: 134–135.

115 Blok JL, van Hattem S, Jonkman MF, Horváth B. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. *Br J Dermatol* 2013; **168**: 243–252.

116 Lee CS, Koo J. A review of acitretin, a systemic retinoid for the treatment of psoriasis. *Expert Opin Pharmacother* 2005; **6**: 1725–1734.

117 Boer J, Nazary M. Long-term results of acitretin therapy for hidradenitis suppurativa. Is acne inversa also a misnomer? *Br J Dermatol* 2011; **164**: 170–175.

118 Matusiak Ł, Bieniek A, Szepietowski JC. Acitretin for hidradenitis suppurativa treatment: a prospective series of 17 patients. *Br J Dermatol* 2014; **171**: 170–174.

119 Verdolini R, Simonacci F, Menon S, *et al.* Alitretinoin: a useful agent in the treatment of hidradenitis suppurativa, especially in women of child-bearing age. *G Ital Dermatol Venereol* 2015; **150**: 155–162.

120 Brocard A, Dréno B. Innate immunity: a crucial target for zinc in the treatment of inflammatory dermatosis. *J Eur Acad Dermatol Venereol* 2011; **25**: 1146–1152.

121 Brocard A, Knol A, Khammari A, Dréno B. Hidradenitis suppurativa and zinc: a new therapeutic approach. *Dermatology* 2007; **214**: 325–327.

122 Badr D, Kurban M, Abbas O. Metformin in dermatology: an overview. *J Eur Acad Dermatol Venereol* 2013; **27**: 1329–1335.

123 Verdolini R, Clayton N, Smith A, *et al.* Metformin for the treatment of hidradenitis suppurativa: a little help along the way. *J Eur Acad Dermatol Venereol* 2013; **27**: 1101–1108.

124 Arun B, Loffeld A. Long-standing hidradenitis suppurativa treated effectively with metformin. *Clin Exp Dermatol* 2009; **34**: 920–921.

125 Jemec GBE. The symptomatology of hidradenitis suppurativa in women. *Br J Dermatol* 1988; **119**: 345–350.

126 Barth JH, Layton AM, Cunliffe WJ. Endocrine factors in pre-and postmenopausal women with hidradenitis suppurativa. *Br J Dermatol* 1996; **134**: 1057–1059.

127 Libecco JF, Bergfeld WF. Finasteride in the treatment of alopecia. *Expert Opin Pharmacother* 2004; **5**: 933–940.

128 Farrell AM, Randall VA, Vafaee T, Dawber RPR. Finasteride as a therapy for hidradenitis suppurativa. *Br J Dermatol* 1999; **141**: 1136–1152.

129 Joseph MA, Jayaseelan E, Ganapathi B, Stephen J. Hidradenitis suppurativa treated with finasteride. *J Dermatolog Treat* 2005; **16**: 75–78.

130 Randhawa HK, Hamilton J, Pope E. Finasteride for the treatment of hidradenitis suppurativa in children and adolescents. *JAMA Dermatol* 2013; **149**: 732–735.

131 Sawers RS, Randall VA, Ebling FJ. Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy. *Br J Dermatol* 1986; **115**: 269–274.

132 Mortimer PS, Dawber RPR, Gales MA, Moore RA. A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol* 1986; **115**: 263–268.

133 Scheinfeld N. Treatment of Hidradenitis Supprurativa Associated Pain with Nonsteroidal Anti-Inflammatory Drugs, Acetaminophen, Celecoxib, Gabapentin, Pegabalin, Duloxetine, and Venlafaxine. *Dermatol Online J* 2013; **19**: 20616.

134 Horváth B, Janse IC, Sibbald GR. Pain management in patients with hidradenitis suppurativa. *J Am Acad Dermatol* 2015; **73**: S47–S51.

135 Schrader AMR, Deckers IE, van der Zee HH, *et al.* Hidradenitis suppurativa: A retrospective study of 846 Dutch patients to identify factors associated with disease severity. *J Am Acad Dermatol* 2014; **71**: 460–467.

136 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

137 Bettoli V, Naldi L, Cazzaniga S, *et al.* Overweight, diabetes and disease duration influence clinical severity in Hidradenitis Suppurativa-Acne Inversa. Evidence from the national Italian Registry. *Br J Dermatol* 2015; **Epub ahead of print**.

138 Vazquez BG, Alikhan A, Weaver AL, *et al.* Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol* 2013; **133**: 97–103.

139 Thomas CL, Gordon KD, Mortimer PS. Rapid resolution of hidradenitis suppurativa after bariatric surgical intervention. *Clin Exp Dermatol* 2014; **39**: 315–318.

140 Boer J. Resolution of hidradenitis suppurativa after weight loss by dietary measures, especially on frictional locations. *J Eur Acad Dermatol Venereol* 2015; **Epub ahead of print**.

141 Kromann C, Ibler KS, Kristiansen V, Jemec GB. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol* 2014; **94**: 553–557.

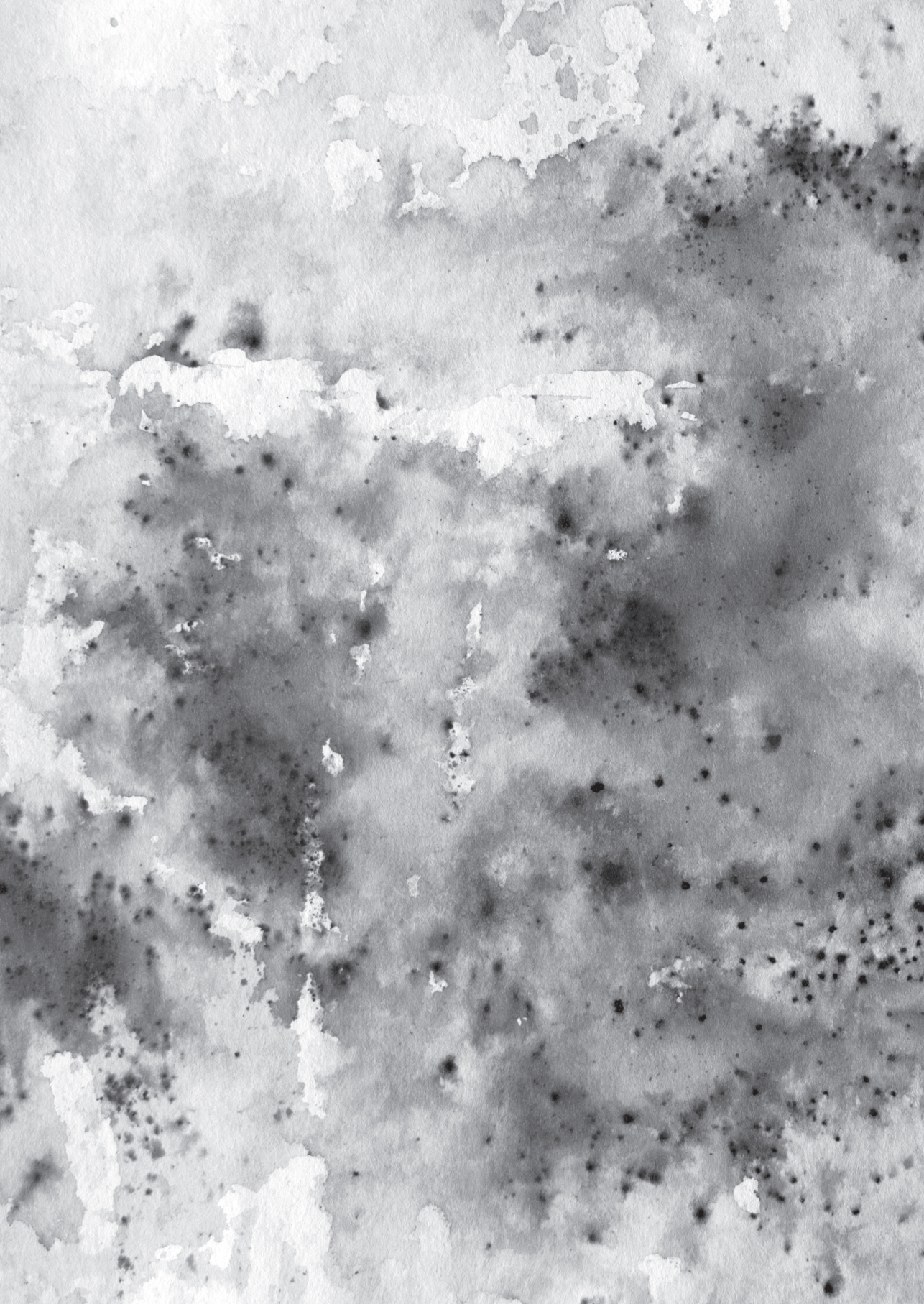
142 Miller IM, Ellervik C, Vinding GR, *et al.* Association of metabolic syndrome and hidradenitis suppurativa. *JAMA dermatology* 2014; **150**: 1273–1280.

143 Matusiak Ł, Bieniek A, Szepietowski JC. Hidradenitis suppurativa and associated factors: still unsolved problems. *J Am Acad Dermatol* 2009; **61**: 362–365.

144 Gaspari AA, Tyring S. New and emerging biologic therapies for moderate-to-severe plaque psoriasis: mechanistic rationales and recent clinical data for IL-17 and IL-23 inhibitors. *Dermatol Ther* 2015; **28**: 179–193.

145 Chiricozzi A, Krueger JG. IL-17 targeted therapies for psoriasis. *Expert Opin Investig Drugs* 2013; **22**: 993–1005.

146 Deeks ED. Apremilast: A Review in Psoriasis and Psoriatic Arthritis. *Drugs* 2015; **75**: 1393–1403.



Chapter 10

Fumarates, a new treatment option for therapy-resistant hidradenitis suppurativa: a prospective open-label pilot study

Inge E. Deckers, Hessel H. van der Zee,
Deepak M.W. Balak, Errol P. Prens

Published in abbreviated form in:
Br J Dermatol. 2015;172:828-829

ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease, without curative treatment; some patients fail all regular treatments. Fumarates are effective in patients with psoriasis, which is attributed to their anti-inflammatory effects. Because in HS patients pro-inflammatory cytokine levels are elevated and are thought to play a key role in the pathogenesis of HS, we hypothesized that fumarates could be effective in patients with HS.

Methods: In a prospective, open-label, pilot study, seven patients with moderate to severe HS, refractory to regular HS drug treatments, were included. Fumarates were administered for a minimal period of 20 weeks in a progressive dosage scheme up to a daily dose of 720 mg dimethylfumarate, following the European psoriasis S3-guidelines. Effectiveness was assessed using a physician's global assessment score.

Results: Three men and four women were included. After 20 weeks of treatment with fumarates, three patients (43%) showed improvement and continued treatment. At 28 weeks one patient, with mild improvement, stopped because of gastrointestinal complaints. Two patients continued treatment for at least one year, remaining clear of inflammatory lesions. In four patients (57%) fumarates were discontinued at week 20 because of lack of efficacy. Most reported side effects were gastrointestinal complaints (57%) and flushing (85%).

Conclusion: Fumarates proved effective in three of seven HS patients, who were refractory to multiple regular HS treatments. Therefore, fumarates can be considered as a therapeutic option in patients who have failed multiple conventional HS therapies.

INTRODUCTION

Hidradenitis suppurativa (HS), or acne inversa, is a chronic, debilitating skin disease, characterized by recurrent inflammatory boils and abscesses, mainly located in areas of the skin folds, such as axillae, groin and perianal regions.[1] HS is common, with an estimated prevalence of 1% in the general population.[2] HS can have a severe negative impact on the quality of life,[3] partly because the disease is difficult to treat. To date, there is no cure for HS. Generally, treatment consists of long-term drug therapy, surgery or both.[1] However, inflammations often flare after the drug treatment is discontinued, and after surgery patients can develop new inflammatory lesions at other or adjacent body areas. Therefore, there is a clear need for effective long-term treatment for HS.

Fumarates have shown to be effective in patients with moderate to severe psoriasis,[4,5] but also in granuloma annulare and cutaneous sarcoidosis.[6,7] This is attributed to their immunomodulatory and anti-inflammatory effects.[8] Because elevated levels of inflammatory mediators, such as interleukin (IL)-1β and tumor necrosis factor alpha (TNF-α), are found in HS and are considered to play an important role in the pathogenesis of HS,[9] we argued that fumarates could also be effective in patients with HS.[10] To investigate this hypothesis, we conducted a prospective, single-center, open-label pilot study, to assess the effectiveness and short-term tolerability of fumarates in patients with moderate to severe HS who were refractory to conventional HS therapies.

SUBJECTS AND METHODS

We conducted a prospective, single-center, open-label pilot study. Seven patients with HS were included from the Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands. The inclusion criteria were age older than 18 years, moderate to severe HS (Hurley stages II or III),[1] recipient of multiple common HS treatments with insufficient or temporary effect. Fumarates were thus considered as a therapy of last resort for these patients. Patients were treated with oral fumarates according to a progressive dosage scheme as recommended by the European S3-guidelines for psoriasis (Table I),[4] for a minimum of 20 weeks, up to a maximum daily dosage of 720 mg dimethylfumarate (DMF). Patient visits were scheduled at baseline, week 4, 8, 12 and 20. At each visit blood count, liver and kidney function, and general urine analysis and urine sediment were collected. All female patients had a pregnancy test at baseline.

At each visit, patients were asked about side effects and clinical photographs were taken. The efficacy outcome was assessed using a physician's global assessment (PGA) compared with baseline: -2, clear worsening; -1, slight worsening; 0, no change; 1, slight improvement; 2, clear improvement; and 3, total clearance of inflammatory lesions.

Table I. Dosage scheme for fumarates (no. of tablets per day)

	Dimethylfumarate	
Week	30 mg[a]	120 mg[b]
1	0 – 0 – 1	–
2	1 – 0 – 1	–
3	1 – 1 – 1	–
4	–	0 – 0 – 1
5	–	1 – 0 – 1
6	–	1 – 1 – 1
7	–	1 – 1 – 2
8	–	2 – 1 – 2
9	–	2 – 2 – 2

Fumarates were administrated as a formulation of enteric-coated tablets containing: [a]30 mg dimethylfumarate and 75 mg monoethylfumarate salts, or [b]120 mg dimethylfumarate and 95 mg monoethylfumarate salts (Apotheek de Magistrale Bereider, Oud-Beijerland, The Netherlands).

RESULTS

The characteristics of the seven patients included are shown in Table II. All patients were active smokers, were overweight with a median body mass index of 33.3 kg/m^2 [interquartile range (IQR): 29.9-41.8], and a median disease duration of 28.0 years [IQR: 18.0-35.0]. All patients were previously treated with topical antibiotics, long-term oral antibiotics (e.g. minocycline, doxycycline, clindamycin, rifampicin). In addition, most were treated with isotretinoin, dapsone, biologics (infliximab, adalimumab or etanercept), or wide local excision of all HS affected skin with primary closure or healing by secondary intention (Table II).

Table II. Patient characteristics and outcomes by physician's global assessment (PGA) score

Patient No.	Sex	Age years	BMI kg/m^2	Hurley stage	Current smoker	Previous treatments	PGA[a] (weeks)				
							4	8	12	20	28
1	M	46	25.0	III	Yes	ABT, ABO, TNF-in (I), iso, WLE	-1	1	0	0	-
2	M	44	41.8	III	Yes	ABT, ABO, TNF-in (A), iso, WLE	0	2	2	2	2
3	F	50	34.6	II	Yes	ABT, ABO, iso, WLE	0	0	1	0	2
4	F	35	29.8	II	Yes	ABT, ABO, TNF-in (A), iso, WLE	-1	1	1	0	1
5	M	53	31.7	II	Yes	ABT, ABO, daps, iso, WLE	-1	-2	0	0	-
6	F	63	33.3	II	Yes	ABT, ABO, TNF-in (I)	0	-1	-1	-1	-
7	F	38	45.7	II	Yes	ABT, ABO, TNF-in (E), iso, WLE	0	0	-2	0	-

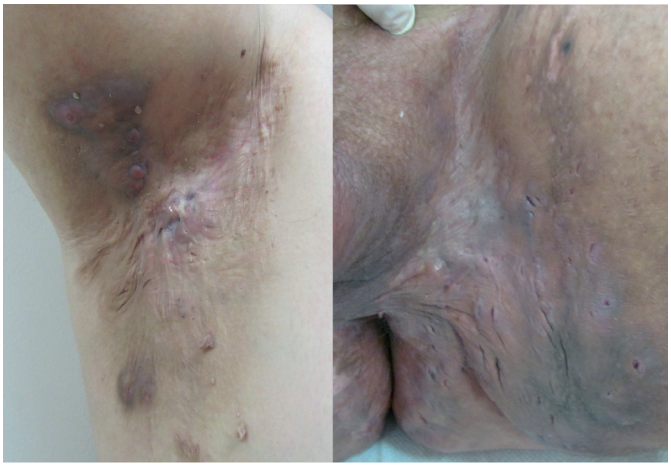
ABT - topical antibiotics; ABO - oral antibiotics; BMI - body mass index; daps - dapson; iso - isotretinoine; TNF-in - tumor necrosis factor alpha inhibitors (I - infliximab, A - adalimumab, E - etanercept); WLE - wide local excision of all HS affected skin
[a] PGA score compared with baseline: -2, clear worsening; -1, slight worsening; 0, no change; 1, slight improvement; 2, clear improvement; and 3, total clearance of inflammatory lesions

Dosage scheme

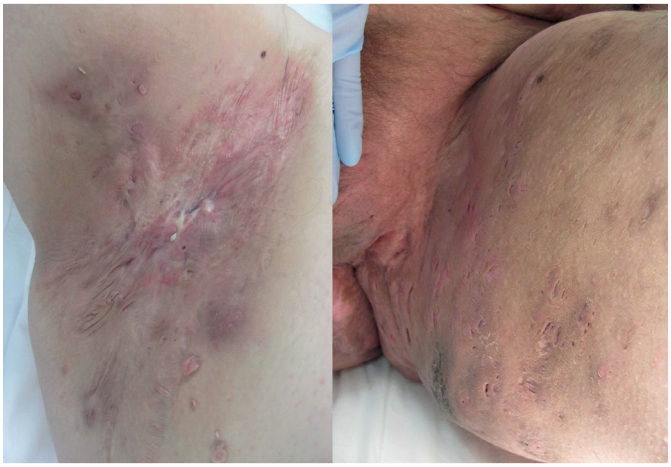
In six patients the standard progressive dosage scheme was followed and therapeutic dosage of 720 mg dimethylfumarate was reached after eight weeks of treatment. In patient 7 the dosage increase was slower because of severe flushing, but she reached the therapeutic dosage after eleven weeks of treatment.

Outcome

After eight weeks of treatment, in three out of seven patients (43%), slight to clear improvement compared with baseline was noted (Table II). At 20 weeks, patient 2 showed



Patient 2 at baseline



Patient 2 after 28 weeks of treatment

Figure 1. Patient 2 at baseline and after 28 weeks of treatment with fumarates, note the decreased skin inflammation.

clear improvement; however, four patients (57%) discontinued fumarates because of lack of efficacy (Table II). As patients 2, 3 and 4 experienced smaller inflammatory lesions that resolved faster, they continued on fumarates, reaching mild to clear improvement after 28 weeks of treatment (Figure 1). Patient 2 and 3 continued therapy, and after one year of treatment both patients still had clear improvement of their HS lesions. Patient 4 stopped at 28 weeks because of persistent diarrhea, showing clear worsening of her HS after discontinuation.

Tolerability

Flushing was mentioned by six patients (85%), four patients (57%) experienced some level of gastrointestinal discomfort (nausea, diarrhea or constipation), and three patients complained about fatigue (43%). Other complaints included pruritus, burning or tingling skin sensation. Side effects resolved in four patients before the 20 week visit. Patient 1 and 5 showed mild lymphopenia, and patient 3 showed mild increased serum creatinine. No significant changes in ALAT, ASAT, γ-GT, leukocytes or eosinophilic granulocytes were observed.

DISCUSSION

This prospective, single-center, open-label pilot study shows that fumarates induced clinically meaningful improvement in three out of seven HS patients, who were previously refractory to conventional HS treatments. Patient 2 and 3 reached clear improvement after 28 weeks of treatment, and continued on fumarates maintaining the clinical response for up to one year. Patient 4 showed mild improvement after 28 weeks, but had to stop because of gastrointestinal complaints. After discontinuation, she showed clear worsening of her HS. Even though a response of three out of seven seems low, we considered it meaningful because these patients were previously unresponsive to multiple common HS treatments.

Common side effects of fumarates are gastrointestinal complaints and flushing.[4] In our study four patients (57%) experienced gastrointestinal complaints and six out of seven patients (85%) experienced flushing. The latter percentage is higher than the earlier reported 31% in psoriasis patients.[6] None of the patients had to stop prematurely due to worsening of blood parameters. Since fumarates are not metabolized through the cytochrome P450-dependent pathways, drug interactions would be less likely and have, to date, not been reported.[11]

The mode of action of fumarates in improving HS is thought to be via its immunomodulatory and anti-inflammatory effects.[8,12] In patients with HS, similar to patients with psoriasis,[13] IL-12 and IL-23 are found abundantly expressed by macrophages in lesional

HS skin.[14] DMF reduces the capacity of dendritic cells and macrophages to produce IL-12 and IL-23.[15] In addition, in the presence of monomethylfumarate, the active metabolite of DMF, dendritic cells produce minimal levels of IL-12p70 and IL-10, and only low levels of TNF-α.[15,16] Finally, in high enough concentrations DMF causes a significant reduction of nuclear factor kappa B (NF-κB),[17] leading to an inhibition of NF-κB-mediated transcription of cytokines such as IL-1, TNF-α and IL-8.[8] In patients with HS, elevated levels of TNF-α, IL-1β and IL-10 are found in lesional skin as well as in unaffected skin,[9] and it has been argued that these cytokines are important in the pathogenesis of HS.[10] We argue that fumarates could be effective in HS through inhibition of these key cytokines.

The limitations of this pilot study are the small sample size, the fact that it was not randomized nor placebo-controlled, and that only patients refractory to multiple conventional HS therapies were included.

In conclusion, this study shows that fumarates induced clinically meaningful improvement in three out of seven patients with recalcitrant moderate to severe HS. Therefore, fumarates can be considered a treatment option for HS, when patients are refractory to regular therapies and no other treatment options are available.

REFERENCES

1 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

2 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

3 Esmann S, Jemec GB. Psychosocial impact of hidradenitis suppurativa: a qualitative study. *Acta Derm Venereol* 2011; **91**: 328–332.

4 Pathirana D, Ormerod AD, Saiag P, *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; **23**: 1–70.

5 Reich K, Thaci D, Mrowietz U, *et al.* Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis–A retrospective study (FUTURE). *J Dtsch Dermatol Ges* 2009; **7**: 603–611.

6 Wollina U. Fumaric acid esters in dermatology. *Indian Dermatol Online J* 2011; **2**: 111–119.

7 Klein A, Coras B, Landthaler M, Babilas P. Off-label use of fumarate therapy for granulomatous and inflammatory skin diseases other than psoriasis vulgaris: a retrospective study. *J Eur Acad Dermatol Venereol* 2012; **26**: 1400–1406.

8 Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends Mol Med* 2005; **11**: 43–48.

9 van der Zee HH, de Ruiter L, van den Broecke DG, *et al.* Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. *Br J Dermatol* 2011; **164**: 1292–1298.

10 van der Zee HH, Laman JD, Boer J, Prens EP. Hidradenitis suppurativa: viewpoint on clinical phenotyping, pathogenesis and novel treatments. *Exp Dermatol* 2012; **21**: 735–739.

11 Thaçi D, Weisenseel P, Philipp S, *et al.* Efficacy and safety of fumaric acid esters in patients with psoriasis on medication for comorbid conditions–a retrospective evaluation (FACTS). *J Dtsch Dermatol Ges* 2013; **11**: 429–435.

12 Onderdijk AJ, Balak DMW, Baerveldt EM, *et al.* Regulated genes in psoriasis skin during treatment with fumaric acid esters. *Br J Dermatol* 2014; **171**: 732–741.

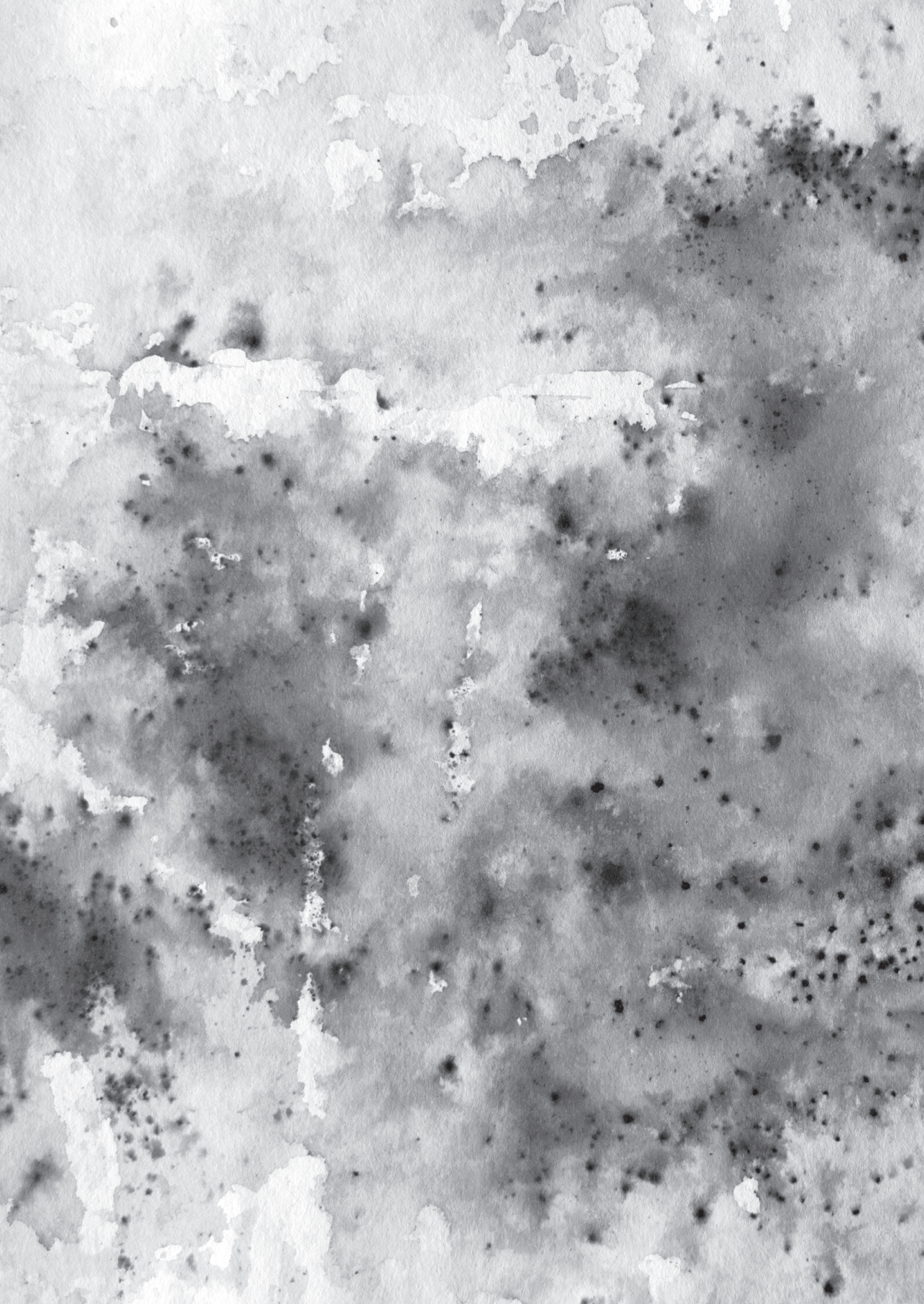
13 Torti DC, Feldman SR. Interleukin-12, interleukin-23, and psoriasis: current prospects. *J Am Acad Dermatol* 2007; **57**: 1059–1068.

14 Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011; **65**: 790–798.

15 Ghoreschi K, Brück J, Kellerer C, *et al.* Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. *J Exp Med* 2011; **208**: 2291–2303.

16 Litjens NHR, Rademaker M, Ravensbergen B, *et al.* Effects of monomethylfumarate on dendritic cell differentiation. *Br J Dermatol* 2006; **154**: 211–217.

17 Gerdes S, Shakery K, Mrowietz U. Dimethylfumarate inhibits nuclear binding of nuclear factor κB but not of nuclear factor of activated T cells and CCAAT/enhancer binding protein β in activated human T cells. *Br J Dermatol* 2007; **156**: 838–842.



Chapter 11

Severe hidradenitis suppurativa treated with wide excision: a meaningful local cure rate and high patient satisfaction

Inge E. Deckers, Yalda Dahi,
Hessel H. van der Zee, Errol P. Prens

Submitted for publication

ABSTRACT

Background: Hidradenitis suppurativa is a chronic inflammatory skin disease, without cure. Surgical treatment under general anesthesia whereby all affected tissue is excised if often needed to achieve remission.

Objectives: To investigate the clinical characteristics, recurrence rate and patient satisfaction in patients with severe HS who had undergone wide surgical excision under general anesthesia.

Methods: The records of patients who had undergone wide surgical excision between 2007 and 2014 at our Dermatology Department, were retrospectively reviewed. In addition patients were sent a questionnaire comprising questions on recurrence and patient satisfaction.

Results: In total 86 patients responded, who had 260 surgical procedures. Mostly the inguinal (n=95, 36.5%) and gluteal/perianal region (n=67, 25.8%) were treated, with secondary-intention healing (59.6%). After a follow-up of on average 3 years, in 50.8% the treated anatomical area remained disease-free, natural disease progression was seen in 12.7%, and recurrence within the surgical scar or less than 0.5 cm from the scar in 36.5% of cases. Most patients were glad that they had the operation (91.8%) and would recommend it to other HS patients (91.8%).

Conclusion: Wide surgical excision induced remission in 50.8% of the affected HS anatomical areas in patients with severe HS. A prospective study is needed to determine the best surgical and closure techniques in severe HS.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease, characterized by painful deep-seated nodules and abscesses mainly located in the inverse body areas, such as the axillary, inguinal and anogenital regions.[1] The prevalence of HS varies from 1% to 4% across Europe.[2,3] HS usually develops after puberty with a peak age of onset in the early twenties, and the prevalence seems to diminish over time;[1,4] also it is more common in women with a female-to-male ratio of 3:1.[3] HS has a major negative impact on the quality of life with a high psychological burden that can lead to isolation.[5]

To date, there is no cure for HS. Patients are generally treated with long-term antibiotics, or in more severe cases with tumor necrosis factor alpha (TNF-α) inhibitors.[5] Surgery gives the highest chance for remission of HS.[1,6] The most common surgical procedures are: incision and drainage, deroofing and limited or wide excision. Incision with drainage is usually performed in acute stages to drain pus from abscesses and to relieve pain, but recurrence rates up to a 100% have been reported.[4,7,8] Deroofing is a surgical technique whereby the lesions are explored using a probe and the roof is excised; it is most effective for recurrent superficial lesions in a mild phase of the disease.[9] In case of a more severe disease, the lesions can be totally excised using limited excision or wide excision surgery, in which smaller excisions tend to have a higher recurrence rate than wider excisions.[4,7]

Even though wide excision is a common surgical procedure for HS, studies in large cohorts of HS patients on the recurrence rate and patient satisfaction are scarce. Therefore, we conducted a retrospective study to investigate the clinical characteristics, recurrence rate and patient satisfaction of HS patients who had undergone wide surgical excision under general anesthesia at our department.

PATIENTS AND METHODS

We identified all patients with HS who underwent wide excision surgery under general anesthesia between 2007 and 2014, at the Department of Dermatology at Erasmus University Medical Center in Rotterdam, The Netherlands. Data were collected from the medical files of the patients, and in addition, for each patient an individual HS-specific questionnaire was made, based on the number of surgical procedures and locations that were treated. The questionnaire, an information letter and informed consent form were sent to the patients. The medical ethical committee of the Erasmus University Medical Center Rotterdam has reviewed and approved the protocol, MEC-2013-596.

Wide excision surgery

Under general anesthesia, using electro-surgery, the HS affected area (clinically recognized by suppurating sinuses, erythema or induration) was completely excised up to the subcutaneous fat or even up to the muscular fascia if necessary. Special care was taken that all sinus tracts were identified and excised. After excision the wounds were left open for healing by secondary intention or (in limited number of cases) were approximated using resorbable stitches or closed via split-skin grafting. When the wounds were left open for secondary intention healing, the wounds were packed with iodine ointment and non-adhesive gauzes followed by bandages. Patients were advised to rinse the wound twice daily and reapply the iodine ointment and non-adhesive gauzes. Most patients were discharged one day after surgery.

Questionnaire

For each patient a questionnaire was made, based on the surgical procedures and the locations treated. Each excised location was counted as an individual surgical procedure. Per surgical procedure patients were asked if they had a recurrence, formulated as a new inflammatory lesion in the treated area or within less than 0.5 cm of the scar.[9] Patients were also asked about the impact of the surgery, whether they were satisfied with the cosmetic results (using a four scale grading system), whether they were glad that they had the operation and if they would recommend this operation to other HS patients (yes or no question).

Data analysis

Results of treatments were based on both medical data files and questionnaires. Statistical analysis of the data was performed using SPSS version 22 for Windows (IBM Corp, Armonk, NY). Continuous data are presented as mean ± standard deviation (SD) or as median with the interquartile range [IQR]. Independent *t*-test or Mann Whitney U test were used to compare continuous variables. Ordinal data are presented as number with the corresponding percentage, and the chi-square test or the Fisher exact test ($n < 5$) were used to compare ordinal data. A *P*-value less than 0.05 was considered statistical significant.

RESULTS

The questionnaire was sent to 120 HS patients, of whom 86 responded (71.7%) of which 50 were males (58.1%) and 36 females (41.9%). Patients responding to the call were more often males and were significantly older, but there was no difference in disease severity according to the Hurley classification, nor in the number of procedures (Table I).

Table I. Characteristics of patients responding and nonresponding to the questionnaire

	Responders (n=86)	Nonresponders (n=34)	*P*-value[a]
Gender, n (%)			0.05
- Male	50 (58.1)	13 (38.2)	
- Female	36 (41.9)	21 (61.8)	
Age years, mean ± SD	46.0 ± 12.9	34.8 ± 11.5	**<0.001**
Hurley stage, n (%)			0.90
- Stage I	12 (14.0)	3 (8.8)	
- Stage II	33 (38.4)	15 (44.1)	
- Stage III	26 (30.2)	10 (29.4)	
- Missing	15 (17.4)	6 (17.7)	
Number of operations, n (%)			0.31
- 1-2	44 (51.1)	19 (55.9)	
- 3-4	27 (31.4)	9 (26.5)	
- 5-6	9 (10.5)	6 (17.6)	
- ≥ 7	6 (7.0)	0	

[a] *P*-value for independend *t*-test, chi-square or Fisher exact test

Patients developed HS at a median age of 20.0 years [IQR: 16.0-30.8], and the mean time between onset and surgery was 18.0 ± 11.8 years. One third had a family history of HS (n=29, 33.7%), and most patients were active smokers (n=57, 66.3%) or ex-smokers (n=21, 24.4%) (Table II).

Performed surgical procedures

The 86 patients underwent in total 122 operations in which 260 locations were treated. The most frequently treated anatomical skin region was the inguinal region (n=95, 36.5%), followed by the genital (n=67, 25.8%) and axillary (n=57, 21.9%) region (Table III). In most cases the wounds were left open after surgery for healing by secondary intention (n=253, 97.3%).

Outcome

The mean follow-up time was 36.2 ± 19.1 months, with a range of 6 up to 79 months. In 90.8% of cases the follow-up was more than a year. After 132 procedures (50.8%) remission was achieved of the operated anatomical area. New inflammatory nodules developed in the same anatomical area after 33 procedures (12.7%), but not in the scar, these were considered as natural disease progression. In 95 cases (36.5%) recurrence occurred in or within less than 0.5 cm from the scar (Table III). Recurrence occurred mostly in younger patients (age at time of operation 39.0 ± 12.4 vs 47.2 ± 12.1 years; $P < 0.001$), and mostly in the genital region, whereas remission more often occurred in the gluteal/perianal region (Figure 1). The median time whereafter recurrence occurred was 6.0 months [IQR:

Table II. General characteristics of included HS patients who had undergone wide surgical excision

	n=86
Gender, n (%)	
- Male	50 (58.1)
- Female	36 (41.9)
Age at disease onset years, median [IQR]	20.0 [16.0-30.8]
Time between onset and operation years, mean ± SD	18.0 ± 11.8
Positive family history of HS, n (%)	29 (33.7)
BMI subgroups,[a] n (%)	
- Normal	27 (31.4)
- Overweight	34 (39.5)
- Obese	25 (29.1)
Smoking status, n (%)	
- Current smokers	57 (66.3)
- Ex-smokers	21 (24.4)
- Nonsmokers	8 (9.3)
Hurley stage, n (%)	
- Stage I	12 (16.9)
- Stage II	33 (46.5)
- Stage III	26 (36.6)
- Missing	15

[a] Body mass index (BMI): Normal weight: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI ≥ 30 kg/m^2

3.0-13.0]. When comparing characteristics of patients who had at least one recurrence with patients without recurrence, there was no difference in gender, smoking history, BMI, or disease severity according to Hurley (data not shown).

Patient satisfaction

Most patients were glad that they had the operation (n=79, 91.9%) and would recommend the surgical procedure to other HS patients (n=79, 91.9%). Two-thirds of the patients were satisfied with the functional and cosmetic results after the operation. However, half of the patients thought that the operation had a medium to major impact (Table IV).

DISCUSSION

In this retrospective study we analyzed data of 260 surgical procedures performed on 86 HS patients between 2007 and 2014. All patients had undergone wide excision surgery under general anesthesia, in which all affected tissue was excised up to the healthy subcutaneous fat or the muscular fascia. Most patients had severe HS (Hurley stage II or III),

Table III. General characteristics of the performed surgical procedures

	n=260
Operation location, n (%)	
- Axillary	57 (21.9)
- Inguinal/femoral	95 (36.5)
- Genital	32 (12.3)
- Gluteal/anal	67 (25.8)
- Other[a]	9 (3.5)
Closure technique, n (%)	
- Secondary intention	253 (97.3)
- Primary closure	5 (1.9)
- Skin graft	2 (0.8)
Follow-up time months, mean ± SD	36.2 ± 19.1
Result after the operation, n (%)	
- Remission of anatomical area	132 (50.8)
- Natural disease progression in anatomical area	33 (12.7)
- Recurrence within the scar, or <0.5cm adjunct	95 (36.5)
Time to recurrence months, median [IQR]	6.0 [3.0-13.0]
Functional properties after surgery,[b] n (%)	
- Improved	44 (30.1)
- No difference	87 (59.6)
- Worsened	15 (10.3)

[a] Other: abdominal, intermammary or submammary region.

[b] The question on limb movement was only asked to patients who had undergone surgery in the axillary or inguinal/femoral area.

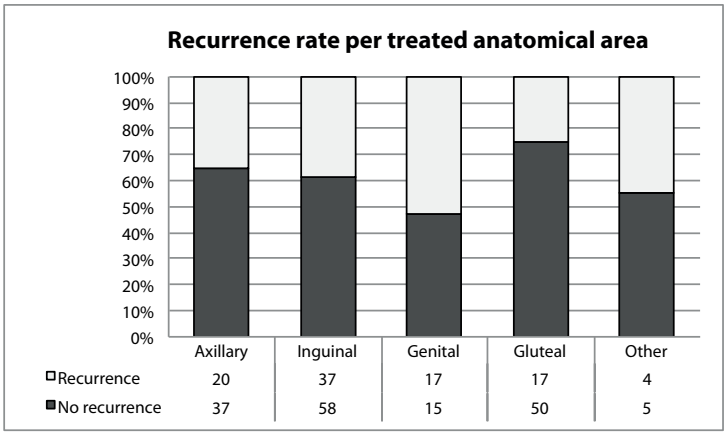


Figure 1. Recurrence rate after wide excision in hidradenitis suppurativa presented as percentage with the corresponding number. Other: abdominal, intermammary or submammary region.

Table IV. Patient satisfaction

	n=86 n (%)
Are you glad you had the operation?	
- Yes	79 (91.9)
- No	7 (8.1)
Would you recommend other patients to have the operations?	
- Yes	79 (91.9)
- No	7 (8.1)
How much impact did the operation have?	
- No impact	10 (11.6)
- Little impact	32 (37.2)
- Medium impact	26 (30.2)
- Major impact	18 (21.0)
Are you satisfied with the cosmetic result?	
- Very satisfied	8 (9.4)
- Satisfied	49 (57.7)
- Unsatisfied	24 (28.2)
- Very unsatisfied	4 (4.7)

which is also supported by the long disease duration of 18 years before they underwent surgery.[10] We did not ask the patients about the reason for the delay before undergoing surgery; however, this would be worthwhile to explore. In our department we have two surgical treatment options for patients with HS: deroofing under local anesthesia for mild HS, or wide excision under general anesthesia for severe or widespread HS. Since men tend to develop more severe HS and they might require wide excision surgery more often, explaining the higher percentage of men in our cohort. Our population was otherwise similar to the overall HS population with regard to smoking status, BMI and family history of HS.[4,5,10,11]

After a mean follow-up time of 3 years, in 63.5% of cases no recurrence was seen within the scar or less than 0.5 cm from the surgical scar; whereas in 36.5% of the surgical procedures a recurrence occurred within the scar. This recurrence rate could be explained by the high number of severely affected HS patients in this study, because patients with more affected body sites are at higher risk of recurrence.[12] However, we did not observe a difference in recurrence rate between patients with different Hurley stages. In addition, 36.5% of the surgical procedures were performed in the inguinal area, which has been shown to have higher recurrence rates than other body regions.[7,13,14] Nonetheless, 92% of the patients were satisfied with the operation and its outcome and would recommend the procedure to other patients with HS, which is comparable to deroofing.[9] Despite the large scars, 67% of the patients were satisfied to very satisfied with the cosmetic results.

Table V. Remission and recurrence rate after surgical treatment for hidradenitis suppurativa

	No.	Follow-up (months)	Method of closure	Remission rate	Recurrence rate
Rompel *et al.*[16]	106 pt	36	Primary, flaps, STSG, per secundam	97.5%	2.5%
Alharbi *et al.*[15]	32 pt	24	Primary, STSG, flaps	81.2%	18.8%
Bieniek *et al.*[12]	57 pt	24	Primary, STSG, flaps, per secundam	59.7%	40.3%
Blok *et al.*[11]	363 op	43	Per secundam	36.5%	29.3%[a]

flaps - different forms of flap coverage have been described in the studies (e.g. local, rotation and transposition); op - operations; STSG - split-thickness skin graft; pt - patients

[a] after 124 (34.2%) operations natural disease progression

Our recurrence rate is similar to other studies in which severe HS patients were surgically treated (Table V). Blok *et al.* analyzed the results of surgery on 113 severe HS patients under general anesthesia. They reported remission in 36%, whereas in 29% recurrence occurred due to irradical surgery and in 34% due to natural disease progression.[11] Bieniek *et al.* performed surgery on 57 HS patients of whom 75% had Hurley stage II or III.[12] They observed complete recovery in 34 patients (60%), whereas partial recovery (31%) or no improvement (9%) was observed in the other 23 patients. Lower recurrence rates (19% and 2.5%) were reported by Alharbi *et al.* and Rompel and Petres. However, of the latter study the disease severity was unknown, also 19% to 38% of the patients needed multiple procedures before [illegible]. Comparing different studies on recurrence rate is impossible,[9,11] since mostly no definition of recurrence was stated, and not all studies, on wide surgical excision, used the same closing technique.

In our study, most wounds were left open for healing by secondary intention. This prevents recurrence due to entrapment of epithelial strands or debris, which can happen after primary closure. Watson *et al.* demonstrated that primary closure had a higher recurrence rate than closure by split-skin graft or local flap cover.[17] Whereas, Rompel and Petres did not observe any differences in recurrence rate between healing by secondary intention, primary suture, local flap plasties, or free skin grafts.[16] A prospective study comparing the different closure techniques is needed to determine which surgical technique is superior to another.

Surgery remains the best option for patients to achieve remission. Antibiotics can initially provide good results; however, up to 62% of the patients who were in remission with antibiotics showed recurrence of the disease after discontinuation.[18,19] This also applies for treatment with anti-TNF biologics. Miller *et al.* treated patients with adalimumab for twelve weeks, with a follow-up of twelve weeks without any treatment. After twelve weeks of treatment a decrease of eleven points in the Sartorius score was observed; however, after the follow-up period, scores had returned to pre-treatment levels.[20] In general, the combination of medical and surgical treatment gives the best results. First

antibiotics or biologics should be given to reduce the inflammation, after which all the sinuses and scarring can be excised during surgery.[5,8]

Even though we report on a large cohort with a long follow-up in which a dermatologist with a long-standing experience with HS surgeries performed the procedures, our study has some limitations. Questionnaires were used in addition to the medical records to determine recurrence. Although the response rate was high (72%), there could be a chance that patients with recurrences responded more often, resulting in an overestimation of the recurrence rate.

Concluding, we report on a sizable cohort of HS patients who had wide surgical excision under general anesthesia. After a mean follow-up period of three years, 51% of the procedures led to remission within the treated anatomical area and in 36% a recurrence was observed. A prospective study comparing different surgical techniques using a uniform definition for recurrence is required to determine which surgical technique produces the best outcome in HS.

REFERENCES

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

2 Jemec GBE, Heidenheim M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential precursor lesions. *J Am Acad Dermatol* 1996; **35**: 191–194.

3 Revuz JE, Canoui-Poitrine F, Wolkenstein P, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol* 2008; **59**: 596–601.

4 Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. *J Am Acad Dermatol* 2009; **60**: 539–561.

5 Zouboulis CC, Desai N, Emtestam L, *et al.* European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; **29**: 619–644.

6 Wollina U, Koch A, Heinig B, *et al.* Acne inversa (Hidradenitis suppurativa): A review with a focus on pathogenesis and treatment. *Indian Dermatol Online J* 2013; **4**: 2–11.

7 Ritz JP, Runkel N, Haier J, Buhr HJ. Extent of surgery and recurrence rate of hidradenitis suppurativa. *Int J Colorectal Dis* 1998; **13**: 164–168.

8 Danby FW, Hazen PG, Boer J. New and traditional surgical approaches to hidradenitis suppurativa. *J Am Acad Dermatol* 2015; **73**: S62–S65.

9 van der Zee HH, Prens EP, Boer J. Deroofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. *J Am Acad Dermatol* 2010; **63**: 475–480.

10 Schrader AMR, Deckers IE, van der Zee HH, *et al.* Hidradenitis suppurativa: A retrospective study of 846 Dutch patients to identify factors associated with disease severity. *J Am Acad Dermatol* 2014; **71**: 460–467.

11 Blok JL, Boersma M, Terra JB, *et al.* Surgery under general anaesthesia in severe hidradenitis suppurativa: a study of 363 primary operations in 113 patients. *J Eur Acad Dermatol Venereol* 2015; **29**: 1590–1597.

12 Bieniek A, Matusiak L, Okulewicz-Gojlik D, Szepietowski JC. Surgical treatment of hidradenitis suppurativa: experiences and recommendations. *Dermatol Surg* 2010; **36**: 1998–2004.

13 Harrison BJ, Mudge M, Hughes LE. Recurrence after surgical treatment of hidradenitis suppurativa. *BMJ* 1987; **294**: 487–489.

14 Velasco AL, Dunlap WW. Pilonidal disease and hidradenitis. *Surg Clin North Am* 2009; **89**: 689–701.

15 Alharbi Z, Kauczok J, Pallua N. A review of wide surgical excision of hidradenitis suppurativa. *BMC Dermatol* 2012; **12**: 9.

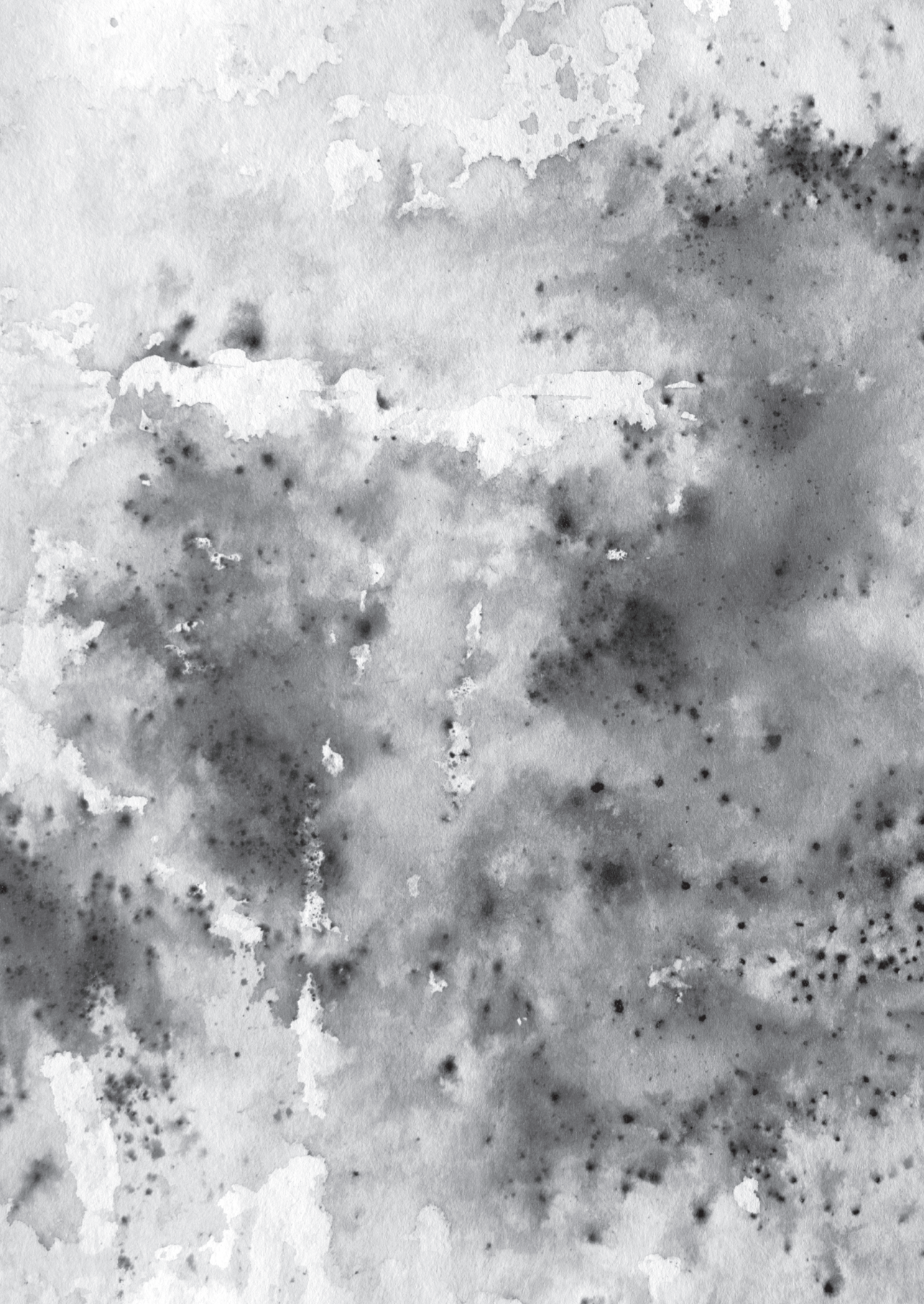
16 Rompel R, Petres J. Long-term results of wide surgical excision in 106 patients with hidradenitis suppurativa. *Dermatol Surg* 2000; **26**: 638–643.

17 Watson JD. Hidradenitis suppurativa—a clinical review. *Br J Plast Surg* 1985; **38**: 567–569.

18 van der Zee HH, Boer J, Prens EP, Jemec GBE. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. *Dermatology* 2009; **219**: 143–147.

19 Join-Lambert O, Coignard H, Jais J, *et al.* Efficacy of rifampin-moxifloxacin-metronidazole combination therapy in hidradenitis suppurativa. *Dermatology* 2011; **222**: 49–58.

20 Miller I, Lynggaard CD, Lophaven S, *et al.* A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. *Br J Dermatol* 2011; **165**: 391–398.



Chapter 12

General discussion
and conclusions

Hidradenitis suppurativa (HS) is a common chronic inflammatory skin disease.[1,2] With a prevalence ranging from 0.05% to 4%, HS should not be called an orphan disease.[3] The prevalence of HS and psoriasis is similar, but HS has a greater negative impact on quality of life.[4] Nonetheless, a pubmed search with the key words "hidradenitis suppurativa" and "acne inversa" gives around 1,250 hits; whereas in a similar search for psoriasis there are 40,000 hits. There are still multiple unanswered questions about the pathogenesis, clinical course, comorbidities and treatment options for HS.[5] This indicates that this debilitating disease does not yet get the attention that it deserves, and therefore still can be considered an orphan disease.

In this thesis we have focused on the clinical aspects of HS. In the first part we determined the prevalence and factors associated with early-onset, disease severity and remission. For the second part of this thesis we have focused on two specific comorbidities of HS, namely anemia and inflammatory bowel disease (IBD), which both have an aberrant immunological reaction as a common factor with HS. The third part of this thesis is about the impact of HS. We investigated the influence of HS on sexual health, and quality of life (QoL), and determined the socioeconomic status of patients with HS relative to dermatological control patients. The last part of this thesis is about the treatments of HS. First, the medical treatment options are reviewed in detail, followed by the effectiveness of fumarates as therapeutic option for HS and finally, the efficacy of wide surgical excision was determined. The main findings of each part of this thesis will be discussed in this last chapter.

PART I: ONSET AND CLINICAL COURSE OF HIDRADENITIS SUPPURATIVA

Generally the onset of HS is after puberty; mostly in de second or third decade of life, with a peak in onset between 20 and 24 years.[2,6,7] Even though pre-pubertal onset has occasionally been described, it has always been thought to be rare.[8,9] Nonetheless, we saw several patients who reported an onset of HS in their early teens or even starting in their infancy. Therefore, we assumed that the prevalence of pre-pubertal onset of HS would be higher than previously suggested. In **Chapter 2** we showed that 66 of the 855 HS patients (7.7%) reported early-onset HS, defined as onset of symptoms before the age of thirteen. We chose this cutoff point based on the mean age of the menarche of 13.5 years in the Netherlands.[10] Since generally puberty occurs later in boys, it is conceivable that most patients with onset before their thirteenth birthday were prepubertal or in early puberty. Our results were shortly after confirmed by Bettoli *et al.*[11] and Blok *et al.*[12] They reported that, respectively, 21% to 38% of their patients had symptoms of HS before the age of sixteen. Our findings that early-onset HS was associated with female sex and a family history of HS were also confirmed.[11,13] The latter suggests that a genetic

predisposition might influence the age of onset of HS.[13,14] Heterozygous mutations in the γ-secretase genes PSENEN, PSEN1, and NCSTN have been found in families in which multiple family members of successive generations had HS,[15,16] although these mutations could not be found in different larger HS populations.[16] Also the exact pathogenic mechanism of the γ-secretase pathway in HS is not yet fully understood.

Interestingly, although smoking is often suggested as a triggering factor for HS, we found that early-onset patients were more often nonsmokers and if they started smoking, this was mostly after they already had symptoms of HS. A likely explanation is that early onset patients were too young to smoke when they had their first HS symptoms, and thereafter were warned not to start smoking because this could worsen their HS symptoms. Also, in the population of Bettoli *et al.* only two of 19 patients under the age of 16 were active smokers.[11]

Although smoking appeared not to be a risk factor in the development of early-onset HS; in **Chapter 3** we demonstrate that patients with more pack-years did have a more severe disease. In the analysis of 846 HS patients we also found that male sex, obesity, and disease duration were associated with disease severity; these findings are in line with previous studies.[7,17,18] We also investigated whether there was a difference in disease characteristics between the male and female patients, and found that female patients had on average an earlier onset of HS and more frequently reported a family history of HS. Also, in female patients the inguinal and mammary regions were more often affected, which confirms the statement that the front part of the body is predominantly involved in women.[14] In men, the backside of the body is more involved,[14] which was confirmed by finding that in male patients, the perianal and gluteal areas were more often involved. Also the atypical sites were more frequently affected in men. This might correspond with the follicular phenotype of Canoui-Poitrine *et al.* in which mostly male patients were severely affected at the ears, chest, armpits and breast.[6]

Another risk factor for severe HS was disease duration, which suggests that disease progression occurs over time. The chronic character of HS was confirmed and studied in more detail in **Chapter 4**. In a retrospective study we asked patients if they still had inflammatory nodules, 22 years after a dermatologist made the diagnosis of HS. In total, 77 of the 127 patients (60.6%) still had active disease. Especially smoking and obese patients still suffered from HS. Of the active smokers only 17% reported remission, versus 33% of the ex- and nonsmokers. Also 23% of the obese patients were disease-free, versus 43% of the nonobese patients. Although nonsignificant, more patients without a family history of HS became disease-free than patients with a first- or second-degree relative suffering from HS (33% vs 48%). These results show that HS is a very chronic disease, but also that a third of the HS patients do become disease-free over the course of time.

Based on the higher remission rates among nonsmokers and nonobese, we argue that patients should be strongly advised to quit smoking and lose weight. It is however im-

portant that patients are informed that smoking cessation does not lead to immediate remission.[17] Our clinical experience is that patients often stop smoking for a brief period (half a year or a year) and do not observe any difference in disease severity or activity, and therefore restart smoking, because 'it does not help anyway'. Therefore, it would be worthwhile explaining to patients that cessation does aid towards remission, but that it takes years to obtain the effect. There is more evidence for the effect of weight loss on remission. Kromann *et al.* interviewed 249 patients who underwent gastric bypass or gastric banding operations to find out if they had HS symptoms before and/or after surgery.[19] Only patients who had lost at least 15% in body mass index (BMI) were included. Before surgery 35 patients reported to have HS, whereas after weight loss 17 patients did not experience HS symptoms anymore (49%), seven reported fewer symptoms (20%) and eleven reported no change or worsening of symptoms (31%).[19] The efficacy of weight loss was further supported by two cases of obese patients who showed major improvement of their HS symptoms after extensive weight loss.[20,21]

Another important side finding in **Chapter 4** was that female patients did not become disease-free after menopause. Of the post-menopausal women 48% reported fewer symptoms, but the remaining did not notice any difference or even experienced worsening of their HS after menopause. Therefore, to prevent disappointment, physicians should not inform female patients that they will become disease-free after menopause.

Conclusion of part one of this thesis:

HS is a chronic and severe disease, which can have its onset before puberty. Twenty-two years after diagnosis, still two-thirds of the patients suffer from HS. Even though a genetic predisposition is associated with early disease onset and might lower the chance of remission, it is not associated with disease severity. Smoking and obesity are not associated with early disease onset, but are strongly associated with disease severity and tend to prevent remission.

PART II: COMORBIDITIES OF HIDRADENITIS SUPPURATIVA

Multiple comorbidities have been reported to be associated with HS; the most frequently reported are: metabolic syndrome (including diabetes mellitus and hypertension), depression, inflammatory bowel disease and spondyloarthropathy.[22,23] In addition, patients with HS often report fatigue, which can be a great burden for the patients.[24,25] A possible cause of this fatigue can be an underlying marked anemia. In **Chapter 5** we presented two cases of patients with severe HS and marked anemia, which resolved after the HS was adequately treated. Tennant *et al.* reported that ten out of their 42 patients with

severe HS (24%) had marked anemia (Hb < 6.3 mmol/L), and suggested that anemia was probably caused by chronic inflammation.[26]

The renal production of erythropoietin is inhibited in the presence of interferon gamma (IFN-γ), interleukin (IL)-1 and tumor necrosis factor alpha (TNF-α).[27,28] These cytokines also reduce erythropoiesis in the bone marrow. Furthermore, IL-1, IL-6, IL-10 and TNF-α can enhance uptake of iron by activated macrophages,[27] whereas TNF-α decreases the intestinal iron absorption,[29,30] both resulting in less iron available for erythropoiesis. In HS, elevated levels of IL-1β, IL-10 and TNF-α have been demonstrated.[31] Therefore, it is possible that these upregulated pro-inflammatory cytokines might contribute to the development of anemia in patients with severe HS. On the other hand, a recent case-control study showed that anemia was not more prevalent in patients with HS than in a population based control group,[32] thus indicating that routinely checking for anemia is not necessary in patients with mild HS. Nonetheless, when patients with severe HS complain about fatigue, anemia should be checked for.

Inflammatory bowel disease (IBD), which is an umbrella term that includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease, caused by an aberrant immunity in a genetically susceptible host.[33] HS and IBD are often associated, and it has been suggested that up to 23% of patients with IBD also suffer from HS.[34–36] In **Chapter 6** we showed that 36 of 1,076 HS patients (3.3%) also suffer from IBD, which is four to eight times more than the prevalence of IBD in the general Northern European population. CD, with a prevalence of 2.5%, was eight to eighteen times more prevalent in patients with HS than in the general population. The association between HS and CD is not surprising as they share multiple similarities:

- Smoking is a triggering factor for both HS and CD, and smokers tend to have a more severe disease than nonsmokers.[7,33] On the other hand, in patients with UC, smoking tends to have a protective effect.[33]
- HS and cutaneous CD share clinical and histological similarities making it difficult to differentiate in certain cases.[37,38] Both can present with perianal inflammatory lesions, abscesses and sinus tract formation. It is not possible to differentiate histologically between HS and CD, because in both diseases diffuse tissue inflammation with epithelioid granulomas is present.[37,38] Cutaneous CD is most likely when only the perianal region is affected and enterocutaneous fistulas are present, whereas concurrent HS is more likely when other body areas are also affected.[39–41]
- HS and IBD both have a genetic basis. In CD, polymorphisms in DNA-regions containing nucleotide oligomerization domain 2 (NOD2) genes are implicated.[33,42] Approximately 30% of the European CD patients have at least one of the three polymorphisms of NOD2.[33] However, in two pilot studies polymorphisms of the CARD15/NOD2 could not be confirmed in patients with HS.[42,43] In a large cohort of IBD patients, a higher frequency of the single-nucleotide polymorphisms SULT1B1,

SULT1E1 and ELOVL7 were found in patients with HS and IBD.[36] In HS, mutations in the γ-secretase genes have been observed, but no causative genes have yet been identified.[16]

- A shared common inflammatory pathway is suggested between HS and IBD.[41,44] In the intestinal mucosa of IBD patients, as well as in lesional skin of HS patients, elevated levels of IL-1β and TNF-α have been observed.[33,45,46] Also the cytokines of the IL-23/Th17 pathway have been found to be elevated in both diseases.[33,46,47]
- Both diseases respond well to treatment with biologics, probably because of the shared immunological pathways. Notably, the effectiveness of TNF-α inhibitors in HS was first described in two CD patients. Their concomitant HS also responded to the infliximab treatment they received for their CD.[48,49] Interestingly, in HS as well as in CD infliximab and adalimumab have shown to be effective, whereas etanercept does not improve symptoms in either two diseases.[23,50]

Patients with HS and IBD did not present with a distinct HS phenotype, we did not observe a difference in disease severity or body regions affected by HS. Dermatologists should therefore ask HS patients about gastrointestinal symptoms. When there is a suspicion of IBD, patients should be referred to a gastroenterologist for further analysis. Also, when patients present with intersphincteric fistulas, an endoscopy or radiological imaging is advisable. Although, we have seen patients with solely HS that presented with intersphincteric fistulas.

Conclusion of part two of this thesis:

Patients with HS that present with severe fatigue should be checked for anemia. Also, referral to a gastroenterologist is advisable when patients present with gastrointestinal symptoms such as recurrent abdominal pain or bloody stool; since 3.3% of the patients with HS have concomitant IBD.

PART III: THE IMPACT OF HIDRADENITIS SUPPURATIVA

HS is a very debilitating disease with a high negative impact on QoL. Relative to other dermatological diseases, patients with HS often have the lowest QoL.[4,51,52] Due to the chronic painful lesions and disfiguring scars, patients often feel embarrassed towards their partners; some reported that their partners had lost interest in sexual activity when they had active lesions or that their sexual life had even completely stopped.[25] Even though HS clearly influences the sexual functioning of the patients, only one study has previously investigated the impact of HS on sexual health. This study among 44 HS patients showed significant impairment of sexual health compared with age-, sex-, and BMI-matched controls.[53]

In **Chapter 7** we confirmed the major impact of HS on sexual health and QoL. In a multicenter cross-sectional study, 300 patients with HS completed multiple sexual health questionnaires and a dermatological quality of life questionnaire. Compared with scores from the literature from healthy men and women, the sexual health scores of the HS patients were far worse.[54,55] Of the female patients 62% had scores corresponding with sexual dysfunction and a high number of men suffered from erectile dysfunction.[55,56] Surprisingly, involvement of the anogenital area or disease severity did not influence sexual health in men or women. Most women stated that HS influenced their sexual health because of its impact on their physical appearance; however, it seems that the physical symptoms of HS can not completely explain the impaired sexual health in HS. Therefore, it is possible that psychological factors also play a role.

The mean Dermatology Life Quality Index (DLQI) score of 12.5 confirms that HS has a very large impact on the patients' QoL.[4,7,24] Low QoL was associated with anogenital involvement and with more active and severe disease. In female patients, QoL was associated with sexual health, but this association was not observed in male patients. Matusiak *et al.* also found that patients with anogenital involvement had a greater impaired QoL;[24] this might be because perianal involvement is associated with a more severe disease, as showed in Chapter 3, and patients with a more severe disease have a lower QoL.[24,51,52,57] Interestingly, female patients with an older age of onset had poorer sexual functioning than females with a young age of onset. Possibly, patients who develop HS when they are already sexually active, are more aware of the changes that occur in their sexual life.[58] Interestingly, a younger age of onset was associated with a lower QoL, which might be the result of the negative correlation between age of onset and disease severity shown in Chapter 2.[52,59] When comparing our results on sexual health and QoL of HS patients with the literature on patients with psoriasis, we saw that HS and psoriasis have similar effects on sexual health,[60,61] whereas the DLQI scores of HS patients were worse than those of patients with psoriasis.[60,62–64]

HS patients also report a great unmet need regarding the attention given by physician to their sexual function. Almost half of the patients indicated that they did not receive enough attention for their sexual function, whereas a third stated that their doctor should have given more attention to their sexual problems. It is possible that physicians do not give enough attention towards sexual problems because of unawareness, shame, difficulty in treatment, limited time, or the complexity of sexual problems.[65] Nonetheless, because of the major impact HS has on the sexual health of patients, physicians should pay more attention towards sexual problems and offer patients psychological support if needed.

Even though multiple studies have shown a diminished QoL in HS, the effect of HS on the professional life of patients varies among studies. Some studies report that HS patients miss only two to three workdays per year,[51,66] whereas Matusiak *et al*. reported

that patients miss on average 34 workdays per year because of their HS.[67] In the latter study, seven out of the 30 interviewed HS patients did not get a promotion, and three even lost their jobs because of HS.[67]

On the basis of our clinical experience, we got the impression that patients with HS had a lower socioeconomic status (SES) than other dermatological patients. Therefore, in **Chapter 8** we compared the SES of HS patients with age and sex matched control patients with other skin diseases. We used a SES indicator developed by Statistics Netherlands, based on the mean household income and mean real estate value per postal code area.[68] The SES of the patients with HS was significantly lower than those of the control patients. Of the HS patients 46% had a low SES and only 15% a high SES, whereas in the control group with other skin diseases 34% had a low SES and 26% a high SES. We presumed that the low SES in HS could be caused by the distressing nature of HS, and therefore we expected that patients with a more severe disease would have a lower SES. Surprisingly, we did not find a difference in disease severity using the Hurley score among the different SES groups. Patients with low SES had more affected body areas, but this was not significant in the multivariable model. Involvement of the axillary region was associated with a lower SES, but for the other body sites this association could not be observed.

We also hypothesized that patients with a young age of onset might have a lower SES, because of missed education or job opportunities; but we did not find a difference in age of onset between the SES groups. The current age was associated with SES, which is not surprising since in general with increasing age people have a higher income and are able to buy a more expensive house than at start of career.[68] We observed that HS patients with a low SES were more often obese. This finding is in line with the results of Lakerveld *et al.*[69] who showed that people from low SES neighborhoods have a higher BMI. Inhabitants from these neighborhoods also showed more obesity-related behavior, such as eating less fruit and vegetables, whereas they drank more sugar-containing drinks.[69] In addition, people with a low SES are also more often smokers.[70,71] Because smoking and obesity are both risk factors for HS,[7,17] it is possible that the unhealthy lifestyle associated with low SES increases the risk of developing HS. However, a large prospective population-based cohort study should be conducted to determine if a low SES truly predisposes HS.

Conclusion of part three of this thesis:

HS is associated with a reduced sexual health, QoL and SES. Impairment in sexual health is associated with female gender and late onset of HS. Important risk factors for a diminished QoL were early disease onset, disease activity and severity. Low SES was associated with axillary involvement, high body mass index, but not with disease severity or age of disease onset.

PART IV: TREATMENTS OF HIDRADENITIS SUPPURATIVA

Over the years multiple treatment options for HS have been suggested; however, none has proven curative. In **Chapter 9** the medical treatment options for HS are reviewed in detail. Based on this review and clinical experience we would like to propose the following medical treatment regime for patients with HS (Figure 1). In mild disease, when patients present with one to four solitary lesions of limited size,[72] one may start with the combination of clindamycin 1% lotion and resorcinol 15% cream.[73–75] Clindamycin lotion should be used as long as the inflammatory lesions are present. Resorcinol cream has shown to reduce the duration of inflammatory lesions.[74,76] In our clinical experience, it can also be used to prevent the formation of new lesions, due to its keratolytic properties it reduces the blockage of the hair follicles.[74,76] For a single recalcitrant inflammatory nodule, intralesional injection with corticosteroids (5 to 10 mg/ml) can induce a rapid reduction.[1,23,76]

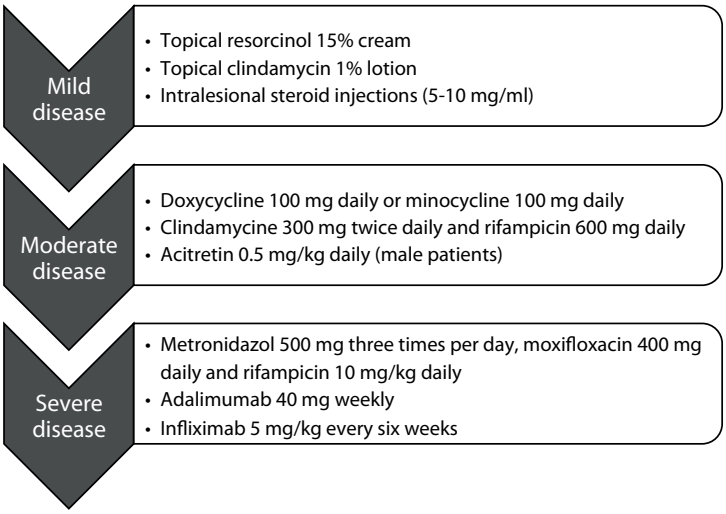


Figure 1. The medical treatment options for patients with hidradenitis suppurativa, ranked by disease severity.

When these local treatments are insufficient or in more widespread HS, oral antibiotics with anti-inflammatory properties are often required. The first step is treatment with antibiotics from the tetracycline group, because of their anti-inflammatory properties and mild side effect profile.[77–79] In our experience doxycycline 100 mg daily or minocycline 100 mg daily can have a good effect in mild HS when given for a minimum of three months.[78,80] One should keep in mind that these antibiotics are mostly effective

because of their immunomodulating effect and that most bacteria cultured in HS are resistant for tetracyclines; therefore, they should not be prescribed to treat bacterial superinfections.[77] The second step is the combination of clindamycin 300 mg twice daily with rifampicin 600 mg daily. This combination therapy has shown to be effective in moderate to severe HS.[81–84] It differs between studies whether rifampicin is given 600 mg daily,[81,82] or 300 mg twice daily.[83,84] From a microbiological point of view it has been suggested that 600 mg once daily would lower the chance of bacterial resistance;[85] however, no studies are available on the effectiveness of different dose schemes in HS. The third step in antibiotic treatment is the combination of metronidazole 500 mg three times per day, moxifloxacin 400 mg daily and rifampicin 10 mg/kg daily.[86] We observed that this combination, when given for minimum of six weeks, can reduce inflammation and induration even in severe HS. However, patients often report side effects, mostly gastrointestinal complaints, headaches or dizziness, leading to dose reduction or early termination.[86,87] For all antibiotics it applies that recurrence is high after discontinuation.[83,86,88]

For male patients presenting with multiple noninflammatory nodules and comedones, treatment with acitretin 0.5 mg/kg can be effective because of its keratolytic properties.[89,90] Because acitretin is highly teratogenic and birth control measures should be used up to three years after treatment, it is less suitable for women in the reproductive age.

When patients have moderate to severe HS and fail most common treatments, biologics are indicated.[23,72,91] Especially adalimumab and infliximab showed to be effective in HS.[72,91,92] Adalimumab 40 mg weekly can be effective in widespread HS;[72] however, in our experience it is less suitable when severe induration is present. Infliximab 5 mg/kg can also reduce severe inflammation and induration when given every six weeks after initiation. However, infliximab is given intravenously mostly in a hospital setting, and therefore it is more time consuming than adalimumab, which patients can administer themselves at home. Both adalimumab and infliximab are expensive drugs, and not all insurance companies are willing to cover the cost. For the future, the cheaper biosimilars might be an option for patients with HS.[93] Even though both adalimumab and infliximab can suppress symptoms for a long time, recurrence can occur during treatment, and often occurs after discontinuation.[23,92,94]

Since none of these treatments are curative for HS, multiple anti-inflammatory drugs have been suggested for HS in small case series of patients with refractory HS.[95–99] In **Chapter 10** we showed the results of therapy with oral fumarates in HS from our open-label pilot study. Seven patients with HS, who were refractory to conventional HS therapies, were treated with fumarates in a progressive dose scheme, up to 720 mg dimethylfumarate for a minimum of 20 weeks. Three patients showed clinical improvement after 20 weeks of treatment, of whom two continued up two years, still being in

remission. However, four patients stopped after 20 weeks because of lack of efficacy and one patient stopped after 28 weeks because of gastrointestinal side effects. Fumarates might be effective because of their immunomodulatory and anti-inflammatory effects, by reducing the production of pro-inflammatory cytokines such as IL-12p70, IL-10 and TNF-α.[100–103] Even though a response of three out of seven seems low, we considered it meaningful because these patients were previously unresponsive to multiple common HS treatments, including antibiotics and biologics. Therefore, fumarates can be considered in patients who are refractory to multiple common therapies and where no other treatment options are available. Patients should be informed about possible side effects during treatment, especially diarrhea and flushing, and the benefits should be weighed against the side effects in each individual patient.

Using medical treatments it is possible to reduce inflammation and suppress symptoms; however, recurrence rates are high after discontinuation.[23,88] Also, sinus formation seldom resolves with drug treatments. Therefore surgical intervention of the existing sinuses and fibrotic tissue is necessary to maintain remission.[1,23,104] In mild cases deroofing has shown to be effective, with a low recurrence rate of 17%.[105] During a deroofing a blunt probe is used to explore the sinuses, whereafter the sinus roof is electrosurgical excised leaving the floor exposed. After carefully examining the margin walls for remaining sinus tracts, the defects is left open for healing by secondary intention.[105,106] However, deroofing is not suited for severe cases.[105]

In **Chapter 11** we reviewed the results of wide surgical excision performed in 86 patients with severe HS. The patients underwent 122 operations, in which 260 locations were treated. During this surgery, performed under general anesthesia, the complete HS affected area (clinically recognized by suppurating sinuses, erythema or induration) was excised using electro-surgery up to the subcutaneous fat or even up to the muscular fascia if necessary. As with deroofing special care was taken that all sinus tracts were identified and excised. After excision the wounds were mostly left open for healing by secondary intention. This way epithelial strands or debris would not be entrapped and wounds could drain.[88]

Using this extensive treatment option we were able to cure the anatomical region in half of the patients, whereas in another 13% the operated area remained free of inflammation but recurrence occurred in the same anatomical region due to natural disease progression. This remission rate might seem low, since other studies report remission rates between the 37% and 98%.[12,107–109] However, all our patients had severe HS with a disease duration of 18 years before they had the operation, resulting in a high disease burden. Direct comparison of our results to other surgical treatment studies is very difficult because different surgical techniques, definitions of recurrence and follow-up times are used. We used the same definition for recurrence as was used in the study on deroofing by van der Zee *et al*;[105] namely, a new inflammatory nodule in the scar or within

0.5 cm adjunct to the scar. Mostly, studies only report the percentage of recurrence, but not whether this new lesion was inside the scar or far distant from the operations site.[107–109] Only Blok *et al.*[12] reported if a recurrence was caused by irradical surgery or due to natural disease progression.[12]

Despite the recurrence rate in our study, patient satisfaction was high. In total, 92% of the patients were glad that they had the operation and would recommend it to other patients with HS. These figures are comparable to patients who had undergone a deroofing procedure.[105] Despite the large scars, 67% of the patients were satisfied to very satisfied with the cosmetic results, making wide surgical excision a good treatment option for patients with severe HS.

Conclusion of part four of this thesis:

Multiple medical treatments are available for HS, such as topical or oral antibiotics, retinoids and biologics. Even though most can suppress symptoms of HS for a long period, they are seldom curative. Fumarates can be effective in refractory HS; however, their effectiveness is limited. Surgery is the most definite treatment for HS; using wide surgical excision, we were able to induce remission in half of the treated anatomical areas.

REFERENCES

1 Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158–164.

2 Revuz JE. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–998.

3 Jemec GBE, Kimball AB. Hidradenitis suppurativa: Epidemiology and scope of the problem. *J Am Acad Dermatol* 2015; **73**: S4–S7.

4 Basra MKA, Fenech R, Gatt RM, *et al.* The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**: 997–1035.

5 Ingram JR, Abbott R, Ghazavi M, *et al.* The Hidradenitis Suppurativa Priority Setting Partnership. *Br J Dermatol* 2014; **171**: 1422–1427.

6 Canoui-Poitrine F, Le Thuaut A, Revuz JE, *et al.* Identification of three hidradenitis suppurativa phenotypes: Latent class analysis of a cross-sectional study. *J Invest Dermatol* 2013; **133**: 1506–1511.

7 Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol* 2009; **161**: 831–839.

8 Mengesha YM, Holcombe TC, Hansen RC. Prepubertal hidradenitis suppurativa: two case reports and review of the literature. *Pediatr Dermatol* 1999; **16**: 292–296.

9 Palmer RA, Keefe M. Early-onset hidradenitis suppurativa. *Clin Exp Dermatol* 2001; **26**: 501–503.

10 Talma H, Schönbeck Y, van Dommelen P, *et al.* Trends in menarcheal age between 1955 and 2009 in the Netherlands. *PLoS One* 2013; **8**: e60056.

11 Bettoli V, Ricci M, Zauli S, Virgili A. Hidradenitis suppurativa–acne inversa: a relevant dermatosis in pediatric age. *Br J Dermatol* 2015; **173**: 1328–1330.

12 Blok JL, Boersma M, Terra JB, *et al.* Surgery under general anaesthesia in severe hidradenitis suppurativa: a study of 363 primary operations in 113 patients. *J Eur Acad Dermatol Venereol* 2015; **29**: 1590–1597.

13 Liy-Wong C, Pope E, Lara-Corrales I. Hidradenitis suppurativa in the pediatric population. *J Am Acad Dermatol* 2015; **73**: S36–S41.

14 Canoui-Poitrine F, Revuz JE, Wolkenstein P, *et al.* Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. *J Am Acad Dermatol* 2009; **61**: 51–57.

15 Pink AE, Simpson MA, Brice GW, *et al.* PSENEN and NCSTN mutations in familial hidradenitis suppurativa (Acne Inversa). *J Invest Dermatol* 2011; **131**: 1568–1570.

16 Pink AE, Simpson MA, Desai N, *et al.* γ-Secretase mutations in hidradenitis suppurativa: new insights into disease pathogenesis. *J Invest Dermatol* 2012; **133**: 601–607.

17 Matusiak Ł, Bieniek A, Szepietowski JC. Hidradenitis suppurativa and associated factors: still unsolved problems. *J Am Acad Dermatol* 2009; **61**: 362–365.

18 Vazquez BG, Alikhan A, Weaver AL, *et al.* Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol* 2013; **133**: 97–103.

19 Kromann C, Ibler KS, Kristiansen V, Jemec GB. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol* 2014; **94**: 553–557.

20 Boer J. Resolution of hidradenitis suppurativa after weight loss by dietary measures, especially on frictional locations. *J Eur Acad Dermatol Venereol* 2015; **Epub ahead of print**.

21 Thomas CL, Gordon KD, Mortimer PS. Rapid resolution of hidradenitis suppurativa after bariatric surgical intervention. *Clin Exp Dermatol* 2014; **39**: 315–318.

22 Kohorst JJ, Kimball AB, Davis MDP. Systemic associations of hidradenitis suppurativa. *J Am Acad Dermatol* 2015; **73**: S27–S35.

23 Zouboulis CC, Desai N, Emtestam L, *et al.* European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; **29**: 619–644.

24 Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol* 2010; **90**: 264–268.

25 Esmann S, Jemec GB. Psychosocial impact of hidradenitis suppurativa: a qualitative study. *Acta Derm Venereol* 2011; **91**: 328–332.

26 Tennant Jr F, Bergeron JR, Stone OJ, Mullins JF. Anemia Associated With Hidradenitis Suppurativae. *Arch Dermatol* 1968; **98**: 138–140.

27 Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352**: 1011–1023.

28 Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. *J Interferon Cytokine Res* 1998; **18**: 555–559.

29 Johnson D, Bayele H, Johnston K, *et al.* Tumour necrosis factor alpha regulates iron transport and transporter expression in human intestinal epithelial cells. *FEBS Lett* 2004; **573**: 195–201.

30 Sharma N, Laftah AH, Brookes MJ, *et al.* A role for tumour necrosis factor alpha in human small bowel iron transport. *Biochem J* 2005; **390**: 437–446.

31 van der Zee HH, de Ruiter L, van den Broecke DG, *et al.* Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. *Br J Dermatol* 2011; **164**: 1292–1298.

32 Miller IM, Johansen ME, Mogensen UB, *et al.* Is hidradenitis suppurativa associated with anaemia?: a population-based and hospital-based cross-sectional study from Denmark. *J Eur Acad Dermatol Venereol* 2015; **Epub ahead of print**.

33 Abraham C, Cho JH. Mechanisms of disease; Inflammatory Bowel Disease. *N Engl J Med* 2009; **361**: 2066–2078.

34 van der Zee HH, de Winter K, Van Der Woude CJ, Prens EP. The prevalence of hidradenitis suppurativa in 1093 patients with inflammatory bowel disease. *Br J Dermatol* 2014; **171**: 673–675.

35 Van der Zee HH, Van Der Woude CJ, Florencia EF, Prens EP. Hidradenitis suppurativa and inflammatory bowel disease: are they associated? Results of a pilot study. *Br J Dermatol* 2010; **162**: 195–197.

36 Janse IC, Koldijk MJ, Spekhorst LM, *et al.* Identification of clinical and genetic parameters associated with hidradenitis suppurativa in inflammatory bowel disease. *Inflamm Bowel Dis* 2016; **22**: 106–113.

37 Attanoos RL, Appleton MAC, Hughes LE, *et al.* Granulomatous hidradenitis suppurativa and cutaneous Crohn's disease. *Histopathology* 1993; **23**: 111–115.

38 Roy MK, Appleton MAC, Delicata RJ, *et al.* Probable association between hidradenitis suppurativa and Crohn's disease: significance of epithelioid granuloma. *Br J Surg* 1997; **84**: 375–376.

39 Yazdanyar S, Miller IM, Jemec GB. Hidradenitis suppurativa and Crohn's disease: Two cases that support an association. *Acta Dermatovenerol Alp Panon Adriat* 2010; **19**: 23–25.

40 Kamal N, Cohen BL, Buche S, *et al.* Features of patients with Crohn's disease and hidradenitis suppurativa. *Clin Gastroenterol Hepatol* 2016; **14**: 71–79.

41 Roussomoustakaki M, Dimoulios P, Chatzicostas C, *et al.* Hidradenitis suppurativa associated with Crohn's disease and spondyloarthropathy: response to anti-TNF therapy. *J Gastroenterol* 2003; **38**: 1000–1014.

42 Nassar D, Hugot JP, Wolkenstein P, Revuz J. Lack of association between CARD15 gene polymorphisms and hidradenitis suppurativa: a pilot study. *Dermatology* 2007; **215**: 359.

43 van Rappard DC, Mekkes JR. Hidradenitis suppurativa not associated with CARD15/NOD2 mutation: a case series. *Int J Dermatol* 2014; **53**: e77–e79.

44 Blazquez I, Gonzalez-Lama Y, Roustan G. Crohn's disease and Hidradenitis suppurativa. An uncommon association that responds to Infliximab. *J Crohn's Colitis* 2013; **7**: e717–e718.

45 Van der Zee HH, de Ruiter L, Boer J, *et al.* Alterations in leucocyte subsets and histomorphology in normal-appearing perilesional skin and early and chronic hidradenitis suppurativa lesions. *Br J Dermatol* 2012; **166**: 98–106.

46 Kelly G, Hughes R, Mc Garry T, *et al.* Dysregulated cytokine expression in lesional and non-lesional skin in Hidradenitis suppurativa. *Br J Dermatol* 2015; **173**: 1431–1439.

47 Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011; **65**: 790–798.

48 Martínez F, Nos P, Benlloch S, Ponce J. Hidradenitis suppurativa and Crohn's disease: response to treatment with infliximab. *Inflamm Bowel Dis* 2001; **7**: 323–326.

49 Katsanos KH, Christodoulou DK, Tsianos E V. Axillary hidradenitis suppurativa successfully treated with infliximab in a Crohn's disease patient. *Am J Gastroenterol* 2002; **97**: 2155–2156.

50 Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *N Engl J Med* 2013; **369**: 754–762.

51 Onderdijk AJ, van der Zee HH, Esmann S, *et al.* Depression in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2013; **27**: 473–478.

52 Wolkenstein P, Loundou A, Barrau K, *et al.* Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. *J Am Acad Dermatol* 2007; **56**: 621–623.

53 Kurek A, Peters EMJ, Chanwangpong A, *et al.* Profound disturbances of sexual health in patients with acne inversa. *J Am Acad Dermatol* 2012; **67**: 422–428.

54 Ter Kuile MM, Brauer M, Laan E. The female sexual function index (FSFI) and the female sexual distress scale (FSDS): psychometric properties within a Dutch population. *J Sex Marital Ther* 2006; **32**: 289–304.

55 McGahuey CA, Gelenberg AJ, Laukes CA, *et al.* The Arizona sexual experience scale (ASEX): reliability and validity. *J Sex Marital Ther* 2000; **26**: 25–40.

56 Lim TO, Das A, Rampal S, *et al.* Cross-cultural adaptation and validation of the English version of the International Index of Erectile Function (IIEF) for use in Malaysia. *Int J Impot Res* 2003; **15**: 329–336.

57 Alavi A, Anooshirvani N, Kim WB, *et al.* Quality-of-life impairment in patients with hidradenitis suppurativa: A canadian study. *Am J Clin Dermatol* 2015; **16**: 61–65.

58 Verschuren JEA, Enzlin P, Dijkstra PU, *et al.* Chronic disease and sexuality: a generic conceptual framework. *J Sex Res* 2010; **47**: 153–170.

59 Von der Werth JM, Jemec GBE. Morbidity in patients with hidradenitis suppurativa. *Br J Dermatol* 2001; **144**: 809–813.

60 Meeuwis KAP, De Hullu JA, Van de Nieuwenhof HP, *et al.* Quality of life and sexual health in patients with genital psoriasis. *Br J Dermatol* 2011; **164**: 1247–1255.

61 Mercan S, Altunay IK, Demir B, *et al.* Sexual dysfunctions in patients with neurodermatitis and psoriasis. *J Sex Marital Ther* 2008; **34**: 160–168.

62 Goulding JMR, Price CL, Defty CL, *et al.* Erectile dysfunction in patients with psoriasis: increased prevalence, an unmet need, and a chance to intervene. *Br J Dermatol* 2011; **164**: 103–109.

63 Herédi E, Rencz F, Balogh O, *et al.* Exploring the relationship between EQ-5D, DLQI and PASI, and mapping EQ-5D utilities: a cross-sectional study in psoriasis from Hungary. *Eur J Health Econ* 2014; **15**: 111–119.

64 De Korte J, Van Onselen J, Kownacki S, *et al.* Quality of care in patients with psoriasis: an initial clinical study of an international disease management programme. *J Eur Acad Dermatol Venereol* 2005; **19**: 35–41.

65 Nusbaum MR, Hamilton C, Lenahan P. Chronic illness and sexual functioning. *Am Fam Physician* 2003; **67**: 347–354.

66 Jemec GBE, Heidenheim M, Nielsen NH. Hidradenitis suppurativa-characteristics and consequences. *Clin Exp Dermatol* 1996; **21**: 419–423.

67 Matusiak Ł, Bieniek A, Szepietowski JC. Hidradenitis suppurativa markedly decreases quality of life and professional activity. *J Am Acad Dermatol* 2010; **62**: 706–708.

68 Van Duin C, Keij I. Sociaal-economische status indicator op postcode niveau. *Maandstatistiek van de Bevolking* 2002; **50**: 32–35.

69 Lakerveld J, Rebah M Ben, Mackenbach JD, *et al.* Obesity-related behaviours and BMI in five urban regions across Europe: sampling design and results from the SPOTLIGHT cross-sectional survey. *BMJ Open* 2015; **5**: e008505.

70 Adler NE, Boyce T, Chesney MA, *et al.* Socioeconomic status and health: the challenge of the gradient. *Am Psychol* 1994; **49**: 15–24.

71 Benson FE, Kuipers MAG, Nierkens V, *et al.* Socioeconomic inequalities in smoking in The Netherlands before and during the Global Financial Crisis: a repeated cross-sectional study. *BMC Public Health* 2015; **15**: 469.

72 Kimball AB, Kerdel F, Adams D, *et al.* Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med* 2012; **157**: 846–855.

73 Jemec GBE, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. *J Am Acad Dermatol* 1998; **39**: 971–974.

74 Boer J, Jemec GBE. Resorcinol peels as a possible self-treatment of painful nodules in hidradenitis suppurativa. *Clin Exp Dermatol* 2010; **35**: 36–40.

75 Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. *Int J Dermatol* 1983; **22**: 325–328.

76 Sartorius K, Boer J, Jemec GBE. Topical treatment. In: Hidradenitis Suppurativa (Jemec GBE, Revuz J, Leyden JJ, eds) Springer, 2006: 150–160.

77 Matusiak Ł, Bieniek A, Szepietowski JC. Bacteriology of hidradenitis suppurativa - which antibiotics are the treatment of choice? *Acta Derm Venereol* 2014; **94**: 699–702.

78 Collier F, Smith RC, Morton CA. Diagnosis and management of hidradenitis suppurativa. *BMJ* 2013; **346**: f2121.

79 Ingram JR, McPhee M. Management of hidradenitis suppurativa: a UK survey of current practice. *Br J Dermatol* 2015; **173**: 1070–1072.

80 Alhusayen R, Shear NH. Scientific evidence for the use of current traditional systemic therapies in patients with hidradenitis suppurativa. *J Am Acad Dermatol* 2015; **73**: S42–S46.

81 Gener G, Canoui-Poitrine F, Revuz JE, *et al.* Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. *Dermatology* 2009; **219**: 148–154.

82 Bettoli V, Zauli S, Borghi A, *et al.* Oral clindamycin and rifampicin in the treatment of hidradenitis suppurativa-acne inversa: a prospective study on 23 patients. *J Eur Acad Dermatol Venereol* 2014; **28**: 125–126.

83 van der Zee HH, Boer J, Prens EP, Jemec GBE. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. *Dermatology* 2009; **219**: 143–147.

84 Mendonça CO, Griffiths CEM. Clindamycin and rifampicin combination therapy for hidradenitis suppurativa. *Br J Dermatol* 2006; **154**: 977–978.

85 Sirgel FA, Fourie PB, Donald PR, *et al.* The early bactericidal activities of rifampin and rifapentine in pulmonary tuberculosis. *Am J Respir Crit Care Med* 2005; **172**: 128–135.

86 Join-Lambert O, Coignard H, Jais J, *et al.* Efficacy of rifampin-moxifloxacin-metronidazole combination therapy in hidradenitis suppurativa. *Dermatology* 2011; **222**: 49–58.

87 Muijsers RBR, Jarvis B. Moxifloxacin. *Drugs* 2002; **62**: 967–973.

88 Ellis LZ. Hidradenitis suppurativa: Surgical and other management techniques. *Dermatol Surg* 2012; **38**: 517–536.

89 Matusiak Ł, Bieniek A, Szepietowski JC. Acitretin for hidradenitis suppurativa treatment: a prospective series of 17 patients. *Br J Dermatol* 2014; **171**: 170–174.

90 Boer J, Nazary M. Long-term results of acitretin therapy for hidradenitis suppurativa. Is acne inversa also a misnomer? *Br J Dermatol* 2011; **164**: 170–175.

91 Blok JL, van Hattem S, Jonkman MF, Horváth B. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. *Br J Dermatol* 2013; **168**: 243–252.

92 Grant A, Gonzalez T, Montgomery MO, *et al.* Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol* 2010; **62**: 205–217.

93 Reinisch W, Smolen J. Biosimilar safety factors in clinical practice. *Semin Arthritis Rheum* 2015; **44**: S9–S15.

94 Miller I, Lynggaard CD, Lophaven S, *et al.* A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. *Br J Dermatol* 2011; **165**: 391–398.

95 Rose R, Goodfield M, Clark S. Treatment of recalcitrant hidradenitis suppurativa with oral cyclosporin. *Clin Exp Dermatol* 2006; **31**: 154–155.

96 Bianchi L, Hansel K, Stingeni L. Recalcitrant severe hidradenitis suppurativa successfully treated with cyclosporine A. *J Am Acad Dermatol* 2012; **67**: e278–e279.

97 Kaur MR, Lewis HM. Hidradenitis suppurativa treated with dapsone: a case series of five patients. *J Dermatolog Treat* 2006; **17**: 211–213.

98 Yazdanyar S, Boer J, Ingvarsson G, *et al.* Dapsone therapy for hidradenitis suppurativa: a series of 24 patients. *Dermatology* 2011; **222**: 342–346.

99 Nazary M, Prens EP, Boer J. Azathioprine Lacks Efficacy in Hidradenitis Suppurativa: A retrospective study of 9 patients. *Br J Dermatol* 2015; **Epub ahead of print**.

100 Onderdijk AJ, Balak DMW, Baerveldt EM, *et al.* Regulated genes in psoriasis skin during treatment with fumaric acid esters. *Br J Dermatol* 2014; **171**: 732–741.

101 Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends Mol Med* 2005; **11**: 43–48.

102 Ghoreschi K, Brück J, Kellerer C, *et al.* Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. *J Exp Med* 2011; **208**: 2291–2303.

103 Litjens NHR, Rademaker M, Ravensbergen B, *et al.* Effects of monomethylfumarate on dendritic cell differentiation. *Br J Dermatol* 2006; **154**: 211–217.

104 Wollina U, Koch A, Heinig B, *et al.* Acne inversa (Hidradenitis suppurativa): A review with a focus on pathogenesis and treatment. *Indian Dermatol Online J* 2013; **4**: 2–11.

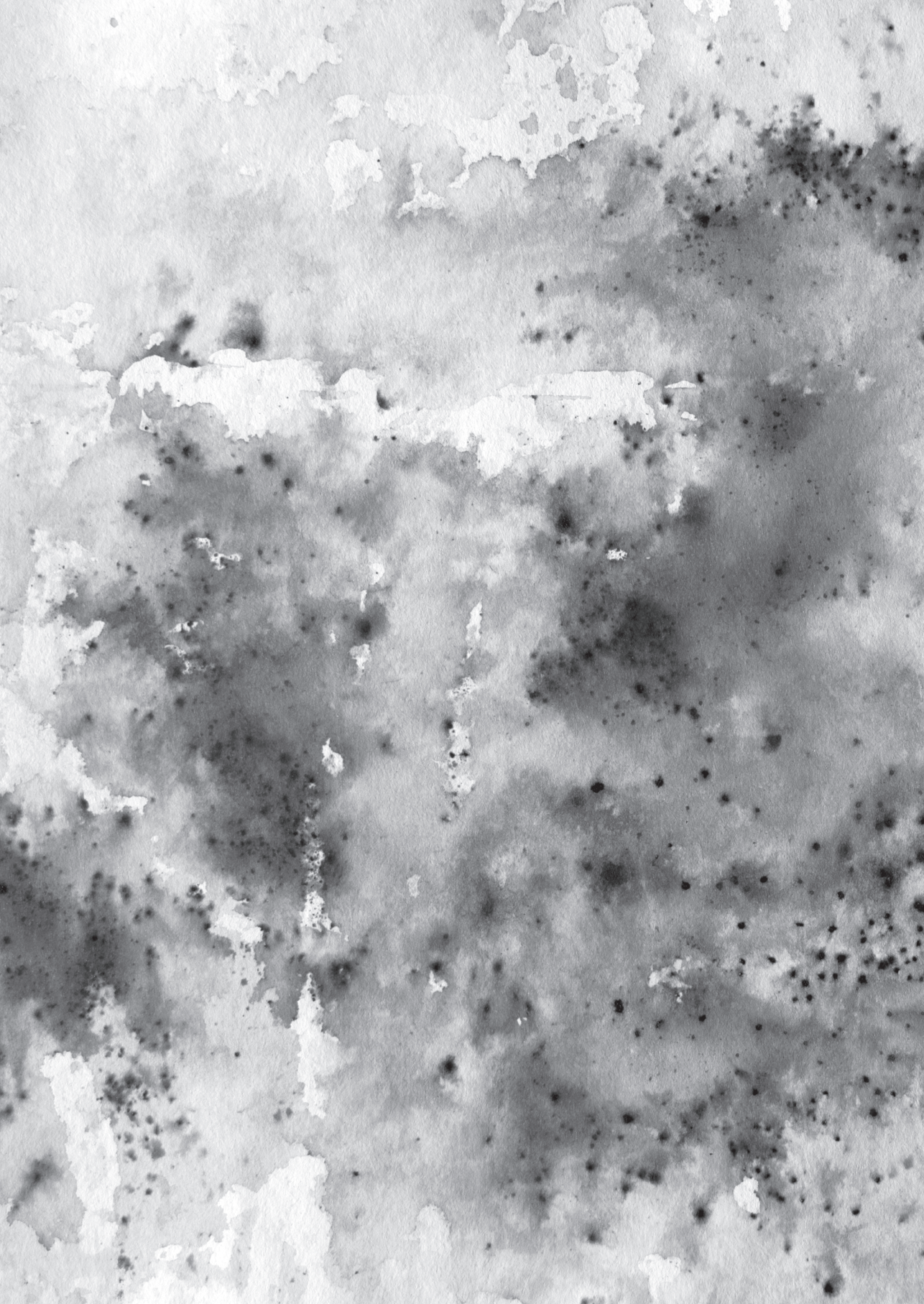
105 van der Zee HH, Prens EP, Boer J. Deroofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. *J Am Acad Dermatol* 2010; **63**: 475–480.

106 Hattem S, Spoo JR, Horváth B, *et al.* Surgical treatment of sinuses by deroofing in hidradenitis suppurativa. *Dermatol Surg* 2012; **38**: 494–497.

107 Rompel R, Petres J. Long-term results of wide surgical excision in 106 patients with hidradenitis suppurativa. *Dermatol Surg* 2000; **26**: 638–643.

108 Alharbi Z, Kauczok J, Pallua N. A review of wide surgical excision of hidradenitis suppurativa. *BMC Dermatol* 2012; **12**: 9.

109 Bieniek A, Matusiak L, Okulewicz-Gojlik D, Szepietowski JC. Surgical treatment of hidradenitis suppurativa: experiences and recommendations. *Dermatol Surg* 2010; **36**: 1998–2004.



Chapter 13

Summary / Samenvatting

SUMMARY

Chapter 1 gives a general introduction to this thesis. Hidradenitis suppurativa (HS) is a chronic, debilitating skin disease with prevalence of 1% in Europe. The disease is characterized by painful inflammatory nodules, abscesses, sinus tract formation and scarring. The lesions are mainly located in the inverse body areas, such as the axillae and groin. The pathogenesis of HS is still not fully understood, but is probably multifactorial. The primary event is thought to be infundibular hyperkeratosis, causing follicular occlusion, followed by rupture of the hair follicle with an inflammatory response. Multiple factors have been associated with HS, especially smoking and obesity. More recently, a genetic background and an aberrant innate immune response have gained more attention as predisposing factors. HS is a profoundly debilitating disease with a great negative impact on the quality of life. HS patients often suffer from depression, have an impaired sexual health, and may have difficulty performing their work duties. To date, there is no cure for most patients; treatment often consists of a combination of drug treatments and surgery. In this thesis we have focused on the clinical aspects of HS. In the first part we determined the prevalence and factors associated with early onset, disease severity and remission. In the second part we studied two specific comorbidities of HS, namely anemia and inflammatory bowel disease. In the third part we discussed the impact of HS on quality of life, sexual health and socioeconomic status. For the last part of this thesis we have focused on the treatment options of HS.

In **chapter 2** we determined the prevalence of early-onset HS. We found that 66 of the 855 patients (7.7%) reported onset of HS before the age of thirteen. Patients with early-onset HS more often had a family history of HS (55.6% vs 34.2%; OR 2.1, 95% CI 1.2-3.6; $P = 0.006$), suggesting that a genetic predisposition might influences the age of onset. Also, early-onset patients developed inflammatory lesions at more body sites than patients with normal-onset HS (OR 3.0, 95% CI 1.8-4.9; $P < 0.001$), whereas the distribution of the Hurley stages showed no difference between the two groups (OR 1.1, 95% CI 0.7-1.8; $P = 0.72$). Surprisingly, early-onset patients were more often nonsmokers (27.3% vs 14.3%; $P = 0.01$) or began smoking after the onset of HS. Our results suggest that early-onset HS is not as rare as always believed. Patients with early-onset HS should be closely monitored and receive appropriate treatments in order to prevent extention of the disease.

In **chapter 3** we sought to identify disease-related factors associated with disease severity, sex, and family history. To do so, we collected data of 846 patients with HS. Of these patients, 45.5% had Hurley stage I, 41.5% had Hurley stage II, and 13.0% had Hurley stage III. We found that disease severity was associated with male sex (OR 2.11; $P < 0.001$),

disease duration (OR 1.03; $P < 0.001$), body mass index (OR 1.03; $P = 0.01$), smoking pack-years (OR 1.02; $P = 0.001$); and axillary (OR 2.24; $P < 0.001$), perianal (OR 1.92; $P < 0.001$), and mammary lesions (OR 1.48; $P = 0.03$). Female patients appeared to have an earlier onset of HS, were more often affected at the inguinal and mammary region, and more frequently had a family history of HS. Male patients were more often affected at the gluteal, perianal and atypical regions (e.g. ears, chest, back). Patients with a family history of HS had on average an earlier disease onset, a longer disease duration, and had a more extensive disease. These severity risk factors could help physicians to select patients who need close monitoring and who would benefit from early, aggressive therapy, although it remains to be shown whether disease progression can be prevented in this way.

In **chapter 4** we described the long-term prognosis and the clinical course of HS and its association to known risk factors. Through a postal questionnaire 212 HS patients were invited to participate in the study. All patients were diagnosed by a dermatologist. The mean follow-up time after diagnosis was 22 years (range 12-32). In total, 129 patients returned valid questionnaires (60.8%). Remission was reported by 39.4% and improvement by 31.5% of the patients, but 20.5% reported unchanged severity and 8.7% experienced disease worsening. More nonsmokers reported remission (48.5%) than active smokers (28.8%), suggesting that the chance of remission was greater in patients who did not smoke or had stopped smoking. We also found a higher proportion of nonobese patients (44.8%) reporting remission than obese patients (22.6%), which further supports the importance of weight loss in patients with HS. This study supports the previous finding that HS is a very chronic disease, but that changing lifestyles (smoking cessation and weight loss) might aid towards disease remission.

In **chapter 5** we presented two cases of severe HS with debilitating fatigue, based on chronic marked anemia. The anemia and associated fatigue were disease activity dependent and resolved after adequate treatment of the extensive HS lesions. We argue that the chronic inflammation with elevated levels of circulating pro-inflammatory cytokines and the continuous sanguineous drainage from the HS lesions, might contribute to the development of anemia. Therefore, it is important to keep in mind that fatigue in patients with HS can be caused by anemia, which is reversible after adequate treatment of the HS.

In **chapter 6** we determined the prevalence of inflammatory bowel disease (IBD) in patients with HS. In addition, we investigated whether patients with HS and IBD had a distinct HS phenotype. In total, 1,076 HS patients were asked during consultation whether they had IBD. The medical files of the affirmative responders were checked to confirm the diagnosis of IBD. We found a prevalence of IBD of 3.3% in our HS cohort, which is four

to eight times higher than in the general northern European population. Most of the patients had Crohn's disease (27/36), which is not surprising since HS and Crohn's disease share various similarities. They both have a clinical course with periods of exacerbations and remission, and respond to tumor necrosis factor alpha inhibitors. In both diseases an aberrant immunity is thought to play an important role in the pathogenesis. Patients with HS and IBD did not present a distinct HS phenotype, since we only observed a difference in body mass index, but not in gender, family history of HS, smoking status, disease severity, or body regions affected.

In **chapter 7** we investigated the quality of life (QoL) in patients with HS with a focus on sexual health. In total, 916 HS patients received an invitation to participate in this multicenter cross-sectional survey, of whom 300 patients completed the questionnaires. HS patients showed a diminished sexual health and QoL (Female Sexual Functioning Index score: 21.6 ± 9.6, International Index of Erectile Function score: 49.7 ± 20.7, Arizona Sexual Experience scale: 16.7 ± 5.3 and Dermatology Life Quality Index score: 12.5 ± 7.5). Sexual health was associated with QoL in women but not in men. Female gender and late onset of HS were associated with poor sexual function. Impairment of QoL was associated with anogenital involvement, early onset of HS, disease severity and disease activity. This study confirms that HS is associated with an impaired sexual health and QoL. Physicians should ask HS patients about their sexual functioning and, when needed, offer them psychological support.

In **chapter 8** we determined the socioeconomic status (SES) in patients with HS relative to control patients, and whether specific clinical HS characteristics correlate with SES. Data were collected of patients with HS and sex and age matched dermatological patients in a 1:2 ratio. The SES was based on an indicator developed by Statistics Netherlands, which was derived from the mean household income and real estate value on neighborhood level. The SES distribution among 1,018 HS patients was significantly lower (low SES: 46.4%, medium SES: 39.0%, high SES: 14.6%), than among 2,039 age and sex matched dermatological control patients (low SES: 34.3%, medium SES: 40.1%, high SES: 25.6%; $P < 0.001$). In HS patients, low SES was associated with axillary involvement (OR 1.42, 95% CI 1.02-1.99), high body mass index (OR 1.03, 95% CI 1.01-1.06) and lower age (OR 0.98, 95% CI 0.97-0.99), but not with disease severity according to Hurley or age of onset. In the general population, a low SES is associated with an unhealthy lifestyle such as smoking and obesity, therefore low SES might be a risk factor for developing HS. However, a prospective cohort study is needed to determine causality.

Chapter 9 is a comprehensive review on the medical treatments of HS and their mode of action. In mild disease, clindamycin lotion or resorcinol cream can give long-term

remission. In more severe HS, oral antibiotics are often needed. Their effectiveness in HS is mostly based on their anti-inflammatory properties and to lesser extent on their anti-bacterial effects. Antibiotics from the tetracycline group are often first-line systemic options. In moderate to severe HS, the combination of clindamycin with rifampicin is often effective; but for all antibiotics, recurrence rates are high after discontinuation. Retinoids can be a more long-term treatment option; especially acitretin has shown to be effective in HS due to its keratolytic properties. However, because retinoids are highly teratogenic, they are less suited for females in the reproductive age. When patients fail to respond to most common treatments and have moderate to severe HS, treatment with biologics, such as infliximab and adalimumab, is indicated. Even though biologics are seldom curative in HS, they can suppress the symptoms and can often be given for a prolonged period. Multiple other anti-inflammatory drugs have been suggested for HS, such as dapsone, azathioprine or cyclosporine. However, their effectiveness in HS is based on small case series with varying results. Besides medical treatment, lifestyle changes are important in the treatment of HS. Patients should be strongly encouraged to reduce weight and quit smoking.

In **chapter 10** we reported on the effectiveness of fumarates in patients with moderate to severe HS in a prospective, open-label, pilot study. Seven patients, who were previously refractory to regular HS treatments, were treated with fumarates for 20 weeks in a progressive dosage scheme up to a daily dose of 720 mg dimethylfumarate. After 20 weeks of treatment, three patients (43%) showed improvement and continued treatment. At 28 weeks one patient, with mild improvement, stopped because of gastrointestinal complaints. Two patients continued treatment for at least one year, remaining clear of inflammatory lesions. In four patients (57%) fumarates were discontinued at week 20 because of lack of efficacy. Most reported side effects were gastrointestinal complaints (57%) and flushing (85%). Fumarates are effective in patients with psoriasis, which is attributed to their anti-inflammatory effects. In HS patients, pro-inflammatory cytokines levels are elevated and are thought to play a key role in the pathogenesis of HS. Therefore, fumarates might also be effective in patients with HS.

In **chapter 11** we investigated the clinical characteristics, recurrence rate and patient satisfaction of patients with severe HS who had undergone wide surgical excision under general anesthesia. The medical files were retrospectively reviewed and patients were sent a questionnaire comprising questions on recurrence and patient satisfaction. In total 86 patients responded, who had undergone a total of 260 surgical procedures. The inguinal (n=95, 36.5%) and gluteal/perianal region (n=67, 25.8%) were mostly treated. In general, the wounds were left open for secondary intention healing (97.3%). After a mean follow-up of 3 years, in 50.8% the treated anatomical area remained disease-free;

natural disease progression was seen in 12.7%, and recurrence within the surgical scar or less than 0.5 cm from the scar in 36.5% of cases. Most patients were glad that they had the surgery (91.8%) and would recommend it to other HS patients (91.8%). This makes wide surgical excision a good treatment option for patients with severe HS.

In **chapter 12** the results of all studies in this thesis are discussed. We showed that HS is a chronic and severe disease that can even develop during childhood. Although we found that a genetic predisposition was associated with early disease onset and might lower the chance of remission, it was not associated with disease severity. Smoking and obesity were not associated with early disease onset, but they were strongly associated with disease severity and tended to prevent remission. HS patients can develop anemia of chronic disease, and therefore anemia should be checked for in patients who present with fatigue. HS is also associated with IBD; in our HS cohort we found that 3.3% of patients had concomitant IBD. This is four to eight times higher than in the general population. HS has a great impact on the lives of patients; we showed that HS is associated with a diminished sexual health, QoL and SES. Impairment in sexual health was associated with female gender and late onset of HS. Early disease onset, disease activity and severity were risk factors for a diminished QoL. Low SES was associated with axillary involvement, high body mass index, and low age, but not with disease severity or age of onset. Multiple medical treatments are available for HS, such as topical or oral antibiotics, retinoids and biologics. Even though most can suppress symptoms of HS for a long period, they are seldom curative. Fumarates can be effective in refractory HS; however, their effectiveness is limited. Surgery is the most definite treatment for HS; using wide surgical excision we were able to induce remission in half of the treated anatomical areas.

SAMENVATTING

Hoofdstuk 1 geeft een algemene inleiding van dit proefschrift. Hidradenitis suppurativa (HS) is een chronische, invaliderende, huidziekte met een prevalentie van 1% in Europa. De ziekte wordt gekenmerkt door pijnlijke inflammatoire nodi en abcessen, gevolgd door sinusvorming en verlittekening. Met name de lichaamsplooien zijn aangedaan, zoals de oksels en de liezen. De pathogenese van HS is nog niet geheel duidelijk, maar is waarschijnlijk multifactorieel. Er wordt gedacht dat door hyperkeratose van het infundibulum occlusie optreedt van de haarfollikel wat leidt tot ophoping van cellulair debris, waardoor de follikel kan scheuren, gevolgd door een overmatige inflammatoire reactie. Meerdere factoren zijn geassocieerd met HS, met name roken en obesitas. Recentelijk is er meer aandacht gekomen voor een genetische aanleg en een overactieve immuunreactie als uitlokkende factoren voor HS. HS is een invaliderende ziekte met een zeer negatieve invloed op de kwaliteit van leven. Daarnaast lijden HS patiënten vaak aan depressie, hebben zij een verminderde seksuele gezondheid en kunnen zij moeilijkheden ondervinden bij het verrichten van hun werk. Tot op heden bestaat er geen genezing voor HS; meestal bestaat de behandeling uit een combinatie van medicamenteuze en chirurgische behandelingen. In dit proefschrift hebben wij ons gefocust op de klinische aspecten van HS. In het eerste deel hebben we de prevalentie bepaald en gekeken naar factoren die zijn geassocieerd met het op jonge leeftijd ontwikkelen van HS, ziekte-ernst en remissie. Voor het tweede deel hebben we gekeken naar twee specifieke comorbiditeiten van HS, namelijk anemie en inflammatoire darmziekte. Het derde deel gaat over de invloed van HS op seksuele gezondheid, kwaliteit van leven en socioeconomische status. Het laatste deel van dit proefschrift gaat over de behandeling van HS.

In **hoofdstuk 2** hebben we de prevalentie bepaald van patiënten die HS op jonge leeftijd hebben gekregen (early-onset HS). In totaal hebben 66 van de 855 HS patiënten klachten gekregen voor de leeftijd van dertien jaar (7.7%). Patiënten met early-onset HS hebben vaker een positieve familieanamnese voor HS (55.6% vs 34.2%; OR 2.1, 95% CI 1.2-3.6; $P = 0.006$). Dit geeft de indruk dat een genetische predispositie mogelijk invloed heeft op de ontstaansleeftijd van HS. Daarnaast blijkt dat patiënten met early-onset HS op meer locaties HS ontwikkelen dan patiënten met een normale ontstaansleeftijd voor HS (OR 3.0, 95% CI 1.8-4.9; $P < 0.001$). Echter, er is geen verschil gevonden tussen de twee groepen in ziekte-ernst volgens Hurley (OR 1.1, 95% CI 0.7-1.8; $P = 0.72$). Verassend genoeg blijken early-onset patiënten vaker niet-rokers te zijn (27.3% vs 14.3%; $P = 0.01$), en beginnen ze vaak pas met roken nadat ze al klachten hebben van HS. Onze resultaten laten zien dat early-onset HS niet zo zeldzaam is als altijd gedacht. Het is belangrijk om

patiënten die op een vroege leeftijd HS krijgen goed te controleren en ervoor te zorgen dat ze adequate behandeling krijgen om uitbreiding van de ziekte te voorkomen.

In **hoofdstuk 3** hebben we gekeken naar ziekte gerelateerde factoren die geassocieerd zijn met ziekte-ernst, geslacht en positieve familieanamnese voor HS. Hiervoor hebben we data verzameld van 846 patiënten met HS. Van deze patiënten heeft 45.5% Hurley stadium I, 41.5% Hurley stadium II en 13.0% Hurley stadium III. Ziekte-ernst blijkt geassocieerd met het mannelijk geslacht (OR 2.11; $P < 0.001$), ziekteduur (OR 1.03; $P < 0.001$), body mass index (OR 1.03; $P = 0.01$), het aantal gerookte pack-years (OR 1.02; $P = 0.001$); en axillaire (OR 2.24; $P < 0.001$), perianale (OR 1.92; $P < 0.001$), en mammaire laesies (OR 1.48; $P = 0.03$). Bij vrouwelijke patiënten ontstaat HS vaker op jongere leeftijd, zijn zij vaker aangedaan in de liezen en rond de borsten, en hebben zij vaker een positieve familieanamnese voor HS. Bij mannen zijn daarentegen vaker de billen, de perianale regio en atypische locaties aangedaan. Patiënten met een positieve familieanamnese voor HS krijgen vaker HS op een jongere leeftijd, hebben een langere ziekteduur en een uitgebreidere ziekte. Deze risicofactoren voor ziekte-ernst kunnen de arts helpen om patiënten te selecteren die extra geobserveerd moeten worden en mogelijkerwijs baat kunnen hebben bij vroege en agressieve therapie.

In **hoofdstuk 4** hebben we gekeken naar de prognose op de lange termijn, het klinische beloop van HS en hebben we de associatie met bekende risicofactoren beschreven. Door middel van een vragenlijst zijn 212 patiënten met HS benaderd om deel te nemen aan deze studie. Deze patiënten zijn gemiddeld 22 jaar geleden door een dermatoloog gediagnostiseerd met HS. In totaal hebben 129 patiënten de vragenlijst ingevuld teruggestuurd (60.8%). Remissie is door 39.4% van de patiënten gerapporteerd en verbetering door 31.5%. Daarentegen heeft 20.5% van de patiënten aangegeven geen verschil te hebben gemerkt in ziekte-ernst en 8.7% geeft zelfs verergering aan. Niet-rokers zijn vaker in remissie dan actieve rokers (48.5% vs 28.8%) en niet-obese patiënten zijn vaker in remissie dan obese patiënten (44.8% vs 22.6%). Deze studie bevestigt dat HS een chronische ziekte is, maar dat het veranderen van de levensstijl (stoppen met roken en afvallen) kan bijdragen tot remissie.

In **hoofdstuk 5** worden twee patiënten gepresenteerd met ernstige HS en een invaliderende vermoeidheid, als gevolg van chronische bloedarmoede. Anemie en de geassocieerde vermoeidheid zijn ziekteafhankelijk gebleken en zijn verbeterd na adequate behandeling van de HS laesies. Wij denken dat de chronische inflammatie, verhoogde bloedspiegels van pro-inflammatoire cytokines en continue bloederige drainage uit de HS laesie kunnen bijdragen aan het ontstaan van anemie. Daarom is het belangrijk om

rekening te houden met de mogelijkheid dat vermoeidheid bij patiënten met HS veroorzaakt kan worden door anemie, welke reversibel is als de HS goed behandeld wordt.

In **hoofdstuk 6** hebben we de prevalentie bepaald van inflammatoire darmziekten (inflammatory bowel disease; IBD) in patiënten met HS. Daarnaast hebben we gekeken of patiënten met zowel IBD als HS een apart HS fenotype hebben. In totaal is aan 1076 HS patiënten gevraagd of zij IBD hebben en van de patiënten die hier positief op hebben geantwoord zijn de medische dossiers nagekeken. We hebben een prevalentie gevonden van IBD van 3.3% in onze HS populatie, wat vier tot acht keer hoger is dan in de algemene Noord Europese populatie. Patiënten met HS hebben vaker de ziekte van Crohn (27/36) dan colitis ulcerosa (9/36), wat niet verassend is aangezien de ziekte van Crohn en HS veel overeenkomsten hebben. Beide ziektes worden gekenmerkt door periodes van exacerbatie en remissies, reageren goed op tumor necrose factor alfa remmers en bij beide ziektes wordt gedacht dat een afwijkend immuunsysteem een rol speelt in de pathogenese. Patiënten met HS en IBD blijken geen apart HS fenotype te hebben, aangezien enkel een lagere body mass index gevonden is in de patiënten met HS en IBD. Er is geen verschil gevonden in geslacht, genetische predispositie, rookgedrag, ziekte-ernst of lichaamsgebieden aangedaan, tussen HS patiënten met of zonder IBD.

In **hoofdstuk 7** hebben we de kwaliteit van leven onderzocht bij patiënten met HS, waarbij er met name gekeken is naar de seksuele gezondheid. In totaal zijn 916 HS patiënten uitgenodigd om deel te nemen aan deze multicenter cross-sectionele studie, waarvan 300 patiënten de compleet ingevulde vragenlijsten hebben geretourneerd. Patiënten met HS blijken een verminderde seksuele gezondheid en kwaliteit van leven te hebben (Female Sexual Functioning Index score: 21.6 ± 9.6, International Index of Erectile Function score: 49.7 ± 20.7, Arizona Sexual Experience scale: 16.7 ± 5.3 and Dermatology Life Quality Index score: 12.5 ± 7.5). Seksuele gezondheid is geassocieerd met kwaliteit van leven bij vrouwen, maar niet bij mannen. Vrouwelijk geslacht en late ontstaansleeftijd van HS zijn geassocieerd met slecht seksueel functioneren. Verminderde kwaliteit van leven is geassocieerd met laesies in het anogenitaal gebied, vroege ontstaansleeftijd van HS, ziekte-ernst en ziekte activiteit. Deze studie bevestigt dat HS geassocieerd is met een verminderde seksuele gezondheid en kwaliteit van leven. Artsen moeten daarom meer aandacht besteden aan de seksuele gezondheid van hun HS patiënten en zo nodig psychologische hulp aanbieden.

In **hoofdstuk 8** hebben we de socio-economische status (SES) bepaald van patiënten met HS en deze vergeleken met dermatologische controle patiënten. Daarnaast is er gekeken of klinische HS karakteristieken correleren met SES. Data zijn verzameld van HS patiënten en leeftijd en geslacht vergelijkbare controle patiënten in een ratio van 1:2. De

SES is gebaseerd op een indicator ontwikkeld door het Centraal Bureau van de Statistiek, met als basis het gemiddelde huishoudinkomen en WOZ-waarde per postcode gebied. Univariate en multivariate ordinale logistische regressie zijn gebruikt om te bepalen of klinische karakteristieken geassocieerd zijn met SES in de HS patiënten. De SES verdeling blijkt significant lager te zijn bij de 1018 HS patiënten (lage SES: 46.4%, midden SES: 39.0%, hoge SES: 14.6%) in vergelijking met leeftijd en geslacht overeenkomstige controle patiënten (lage SES: 34.3%, midden SES: 40.1%, hoge SES: 25.6%; $P < 0.001$). Een lage SES is bij de HS patiënten geassocieerd met axillaire betrokkenheid (OR 1.42; 95% CI 1.02-1.99), hoge body mass index (OR 1.03; 95% CI 1.01-1.06) en lage leeftijd (OR 0.98; 95% CI 0.97-0.99). Patiënten met HS hebben niet alleen een significant lagere SES dan andere dermatologie patiënten maar ook dan de Nederlandse populatie. Lage SES is geassocieerd met obesitas, maar niet met ziekte ernst. In de algemene populatie is een lage SES geassocieerd met een ongezonde levensstijl zoals roken en overgewicht; lage SES zou daarom mogelijk een risicofactor kunnen zijn voor het ontwikkelen van HS. Een prospectieve cohort studie is echter nodig om causaliteit aan te kunnen tonen.

Hoofdstuk 9 is een uitgebreide review over de medicamenteuze behandelingen van HS. Bij milde ziekte, kunnen clindamycine lotion en resorcinol crème langdurig remissie geven; bij uitgebreidere ziekte zijn orale antibiotica vaak geïndiceerd, waarbij de effectiviteit voornamelijk gebaseerd is op de anti-inflammatoire eigenschappen, en in mindere mate op de antibacteriële werking. Antibiotica uit de tetracycline groep zijn vaak therapie van eerste keus. Bij matige tot ernstige HS is de combinatie van clindamycine met rifampicine vaak effectief. Voor alle antibiotica geldt dat na stoppen het recidief percentage hoog is. Retinoïden zijn een goede lange termijnoplossing voor HS, met name acitretine is effectief gebleken door zijn keratolytische werking. Aangezien retinoïden teratogeen zijn, zijn ze minder geschikt voor vrouwen in de vruchtbare leeftijd. Wanneer patiënten met matige of ernstige HS onvoldoende reageren op de standaard behandelingen, komen ze in aanmerking voor behandeling met biologicals zoals infliximab en adalimumab. Hoewel biologicals zelden genezend zijn, kunnen ze de symptomen deels voor langere tijd onderdrukken en vaak langdurig gegeven worden. Verder zijn er meerdere anti-inflammatoire medicijnen beschreven voor HS, zoals dapson, azathioprine of cyclosporine; de effectiviteit hiervan is echter gebaseerd op kleine patiëntengroepen met wisselende resultaten. Naast de medicamenteuze behandeling is het belangrijk dat patiënten hun levensstijl aanpassen: patiënten moet worden aangeraden te stoppen met roken en af te vallen.

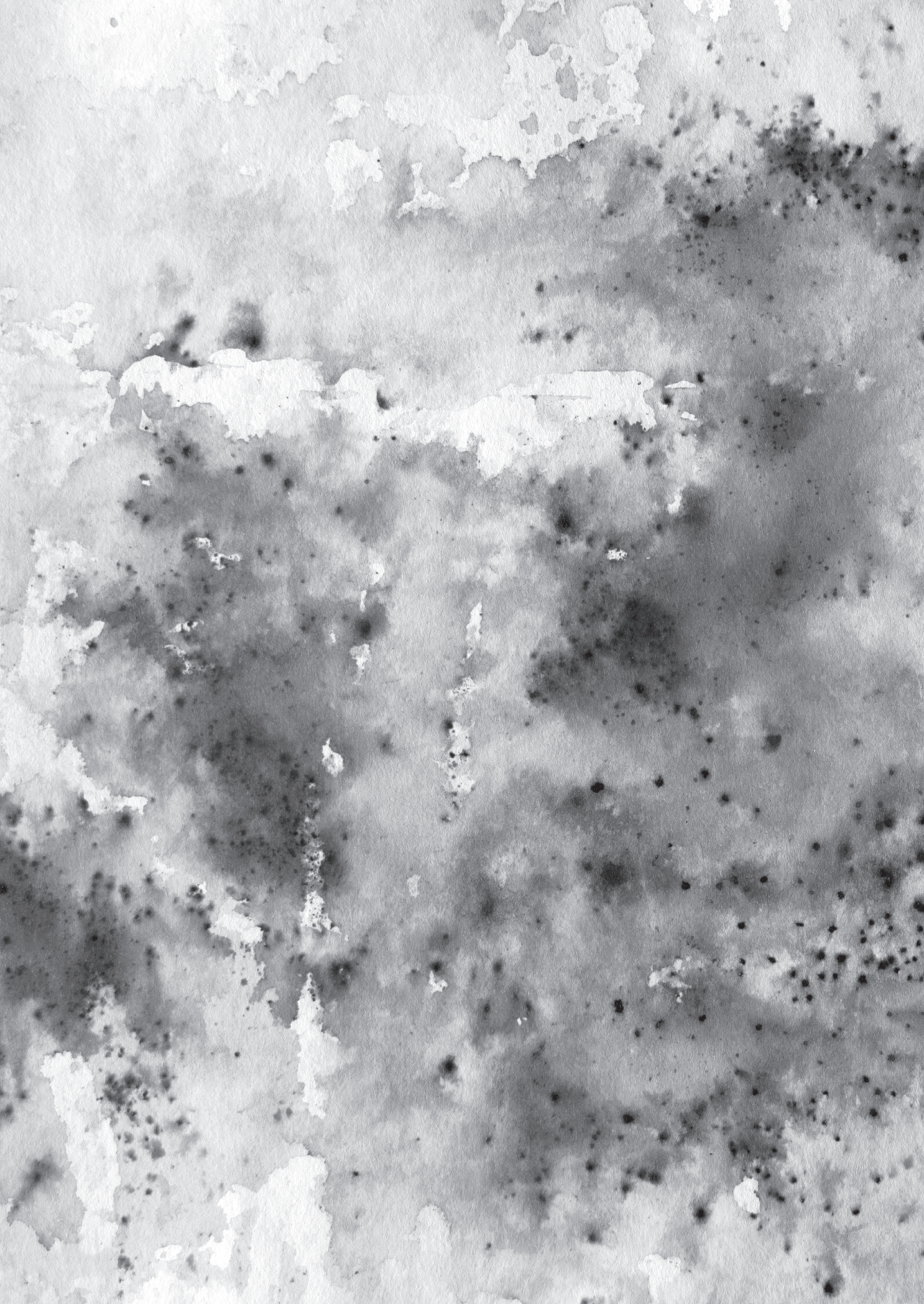
In **hoofdstuk 10** worden de resultaten besproken van het prospectieve open-label pilot onderzoek naar de effectiviteit van fumaarzuur bij patiënten met matige tot ernstige HS. Zeven patiënten die voorheen niet reageerden op reguliere HS behandelingen zijn 20

weken behandeld met fumaarzuur in een oplopende dosis tot 720 mg dimethylfumaraat per dag. Na 20 weken zijn bij drie patiënten (43%) de klachten duidelijke verbeterd en daarom is de behandeling gecontinueerd. Na 28 weken moest één patiënte stoppen in verband met maag/darm klachten. Twee patiënten zijn door gegaan met fumaarzuur en na een jaar hebben zij nog steeds een duidelijke verbetering van hun HS laesies. Vier patiënten stopten na 20 weken vanwege onvoldoende effect (57%). De meest voorkomende bijwerkingen die zijn gemeld zijn maag/darm klachten (57%) en flushing (opvliegers) (85%). Fumaarzuur is effectief in patiënten met psoriasis, wat wordt gewijt aan de anti-inflammatoire effecten van fumaarzuur. Bij patiënten met HS zijn verhoogde bloedspiegels van pro-inflammatoire cytokines gevonden, en waarschijnlijk spelen deze een belangrijke rol in de pathogenese van HS. Daarom zijn fumaraten mogelijk ook effectief in patiënten met HS.

In **hoofdstuk 11** hebben we gekeken naar de klinische karakteristieken, het recidief risico en de tevredenheid van patiënten die behandeld zijn met ruime excisie onder algehele narcose. Hiervoor zijn de dossiers retrospectief bekeken, en zijn patiënten benaderd middels een vragenlijst over mogelijke recidieven en patiënttevredenheid. In totaal hebben 86 patiënten geantwoord die samen 260 chirurgische procedures hebben ondergaan. De inguinale (n=95, 36.5%) en natale regio (n=67, 25.8%) zijn het vaakst geopereerd. Over het algemeen zijn de wonden open gelaten voor genezing per secundam (97.3%). Na een gemiddelde follow-up tijd van drie jaar, is bij 50.8% het geopereerde gebied nog volledig vrij van ontstekingen. Natuurlijke ziekteprogressie wordt gezien bij 12.7%, terwijl recidieven in het litteken of binnen een straal van 0.5 cm van het litteken worden gezien bij 36.5% van de operaties. Patiënten zijn zeer vaak tevreden over de behandeling (91.8%) en zouden de operatie aan andere HS patiënten aanraden (91.8%). Hierdoor is ruime excisie chirurgie een goede optie voor patiënten met een ernstige HS.

In **hoofdstuk 12** worden alle resultaten uit dit proefschrift besproken. We hebben aangetoond dat HS een chronische en ernstige ziekte is die al tijdens de kindertijd kan ontstaan. Hoewel een genetische predispositie geassocieerd is met het vroege ontstaan van de ziekte en mogelijk de kans op remissie verlaagt, is het niet geassocieerd met ziekte-ernst. Roken en overgewicht zijn niet geassocieerd met het vroege ontstaan van HS, maar zijn wel sterk geassocieerd met ziekte-ernst en lijken de kans op remissie te verminderen. HS patiënten kunnen anemie door chronische ziekte ontwikkelen en daarom moet anemie worden uitgesloten bij patiënten met ernstige vermoeidheid. HS is ook geassocieerd met IBD; in ons HS cohort bleek 3.3% van de HS patiënten IBD te hebben. Dit is vier tot acht maal hoger dan in de algemene populatie. HS heeft een negatieve invloed op het leven van patiënten; we hebben aangetoond dat HS is geassocieerd met

een verlaagde seksuele gezondheid, kwaliteit van leven en socio-economische status. Vermindering van seksuele gezondheid is geassocieerd met het vrouwelijke geslacht en het ontwikkelen van HS op latere leeftijd. Risicofactoren voor een verlaagde kwaliteit van leven zijn het op jonge leeftijd ontwikkelen van HS, verhoogde ziekte activiteit en ziekte-ernst. Lage SES is geassocieerd met axillaire laesies, hoge body mass index, en lage leeftijd, maar is niet geassocieerd met ziekte-ernst of de ontstaansleeftijd van HS. Meerdere medicamenteuze behandelingen zijn beschreven voor HS, zoals topicale of orale antibiotica, retinoïden en biologicals. Hoewel deze de ziekte vaak voor langere tijd kunnen onderdrukken zijn ze zelden genezend. Fumaraten blijken effectief bij een aantal patiënten die voorheen niet reageerden op reguliere HS behandelingen, echter hun effectiviteit is gelimiteerd. Chirurgische behandeling is vaak de meest definitieve oplossing voor HS. Door middel van ruime chirurgische excisie is remissie geïnduceerd in de helft van de behandelde anatomische locaties.



Chapter 14

Appendices

Abbreviations
List of co-authors
List of publications
PhD portfolio
Curriculum Vitae
Dankwoord

ABBREVIATIONS

AGI	anogenital involvement
ASEX	Arizona Sexual Experience scale
BD	twice daily
BMI	body mass index
CD	Crohn's disease
CI	confidence interval
CNS	central nervous system
CoNS	coagulase-negative staphylococci
DLQI	Dermatology Life Quality Index
DM	diabetes mellitus
DMF	dimethylfumarates
ES	effect size
FSFI	Female Sexual Function Index
Hb	hemoglobin
HiSCR	Hidradenitis Suppurativa Clinical Response
HS	hidradenitis suppurativa
HS-IBD	patients with hidradenitis suppurativa and inflammatory bowel disease
HSSI	Hidradenitis Suppurativa Severity Index
HS-PGA	Hidradenitis Suppurativa Physician Global Assessment
IBD	inflammatory bowel disease
IIEF	International Index of Erectile Function
IL	interleukin
IQR	interquartile range
MCV	mean corpuscular volume
n	number
NF-κB	nuclear factor kappa B
NOD2	nucleotide oligomerization domain 2
NSAID	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PG	pyoderma gangrenosum
PGA	physicians global assessment
PtGA	patient global assessment
QoL	quality of life
SAPIR	sexually active patients in a relationship
SAPNIR	sexually active patients not in a relationship
SD	standard deviation

SE	sensitivity
SES	socioeconomic status
SP	specificity
TB	tuberculosis
TID	three times daily
TNF-α	tumor necrosis factor alpha
UC	ulcerative colitis
VAS	visual analog scale

LIST OF CO-AUTHORS

Affiliations at the time at which the research was conducted

Deepak M.W. Balak
Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Farida Benhadou
Department of Dermatology, Hôpital Erasme, Université Libre de Bruxelles, Belgium

Jurr Boer
Department of Dermatology, Deventer Hospital, Deventer, The Netherlands

Yalda Dahi
Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Solveig Esmann
Department of Dermatology, Health Science Faculty, Roskilde Hospital, University of Copenhagen, Denmark

Andrea W.M. Evers
Institute of Psychology, Department of Health, Medical and Neuropsychology, Leiden University, Leiden, The Netherlands

Barbara Horváth
Department of Dermatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Ineke C. Janse
Department of Dermatology, University of Groningen, University Medical Center roningen, Groningen, The Netherlands

Gregor B.E. Jemec
Department of Dermatology, Health Science Faculty, Roskilde Hospital, University of Copenhagen, Denmark

Alexa B. Kimball
Department of Dermatology, Harvard Medical School, Boston, Massachusetts, USA

Marjolein J. Koldijk
Department of Dermatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Charles B. Kromann
Department of Dermatology, Health Science Faculty, Roskilde Hospital, University of openhagen, Denmark

Veronique del Marmol
Department of Dermatology, Hôpital Erasme, Université Libre de Bruxelles, Belgium

Anita D. van der Maten
Department of Dermatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Tamar E.C. Nijsten
Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Errol P. Prens
Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Anne M.R. Schrader
Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

Hessel H. van der Zee
Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

LIST OF PUBLICATIONS

In this thesis:

2014 **I.E. Deckers**, H.H. van der Zee, E.P. Prens. Epidemiology of hidradenitis suppurativa: prevalence, pathogenesis, and factors associated with the development of HS.
Curr Derm Rep. 2014;**3**:54-60

2014 A.M.R. Schrader, **I.E. Deckers**, H.H. van der Zee, J. Boer, E.P. Prens. Hidradenitis suppurativa: a retrospective study of 846 Dutch patients to identify factors associated with disease severity.
J Am Acad Dermatol. 2014;**71**:460-467

2014 C.B. Kromann*, **I.E. Deckers***, S. Esmann, J. Boer, E.P. Prens, G.B.E. Jemec. Risk factors, clinical course and long-term prognosis in hidradenitis suppurativa: a cross-sectional study.
Br J Dermatol. 2014;**171**:819-824
* Shared first author

2015 **I.E. Deckers**, H.H. van der Zee, D.M.W. Balak, E.P. Prens. Fumarates, a new treatment option for therapy-resistant hidradenitis suppurativa: a prospective open-label pilot study.
Br J Dermatol. 2015;**172**:828-829

2015 **I.E. Deckers**, H.H. van der Zee, J. Boer, E.P. Prens. Correlation of early-onset hidradenitis suppurativa with stronger genetic susceptibility and more widespread involvement.
J Am Acad Dermatol. 2015;**72**:485-488

2016 **I.E. Deckers**, H.H. van der Zee, E.P. Prens. Severe fatigue based on anaemia in patients with hidradenitis suppurativa: report of two cases and a review of the literature.
J Eur Acad Dermatol Venereol. 2016;**30**:174-175

2016 **I.E. Deckers**, A.B. Kimball. The handicap of hidradenitis suppurativa.
Dermatol Clin. 2016;**34**:17-22

2016 **I.E. Deckers**, E.P. Prens. An update on medical treatment options for hidradenitis suppurativa.
Drugs. 2016;**76**-215-229

2016 **I.E. Deckers**, Y. Dahi, H.H. van der Zee, E.P. Prens. Severe hidradenitis suppurativa treated with wide excision: a meaningful local cure rate and high patient satisfaction.
S*ubmitted*

2016 I.C. Janse, **I.E. Deckers**, A.D. van der Maten, A.W.M. Evers, J. Boer, H.H. van der Zee, E.P. Prens, B. Horváth. Sexual health and quality of life are severely impaired in hidradenitis suppurativa: a multicenter cross-sectional study.
Submitted

2016 **I.E. Deckers**, F. Benhadou, M.J. Koldijk, V. Del Marmol, B. Horváth, J. Boer, H.H. van der Zee, E.P. Prens. Inflammatory bowel disease is common in patients with hidradenitis suppurativa, but not a distinct phenotype; results from a multicenter cross-sectional study.
Submitted

2016 **I.E. Deckers**, I.C. Janse, H.H. van der Zee, T. Nijsten, J. Boer, B. Horváth, E.P. Prens. Hidradenitis suppurativa is associated with a low socioeconomic status: a cross-sectional reference study.
Submitted

Other publications:

2013 **I.E. Deckers***, C.B. van Lee*, R.R. van den Bos, S. Koljenović, K. Munte. Mohs' micrografische chirurgie als behandeling voor het dermatofibrosarcoma protuberans.
Ned Tijdschr Dermatol Venereol. 2013;**23**;645-650
* Shared first author

2015 **I.E. Deckers**, D. Mihajlović, E.P. Prens, J. Boer. Hidradenitis suppurativa: a pilot study to determine the capability of patients to self-assess their Hurley stage.
Br J Dermatol. 2015;**172**:1418-1419

2015 **I.E. Deckers**. Hidradenitis suppurativa, een chronische ziekte met veel pijnlijke ontstekingen.
Cutis Cura. 2015;**2**:32-34

2015 M. Daxhelet, M. Suppa, F. Benhadou, V. Djamei, T. Tzellos, G. Ingvarsson, J. Boer, A. Martorell, J.R. Ingram, N. Desai, A. Nassif, J. Revuz, C. Hotz, V Bettoli, **I.E. Deckers**, G.B. Jemec, E.P. Prens, C.C. Zouboulis, V. Del Marmol. Establishment of a European Registry for hidradenitis suppurativa/acne inversa by using an open source software.
J Eur Acad Dermatol Venereol. 2015 Sep 15 [Epub ahead of print] doi: 10.1111/jdv.13267.

2015 E.P. Prens, **I.E. Deckers**. Pathophysiology of hidradenitis suppurativa: An update.
J Am Acad Dermatol. 2015; **73**(5 suppl 1):S8-11

PHD PORTFOLIO

Name PhD student:	Inge E. Deckers
Department:	Dermatology, Erasmus MC, University Medical Center, Rotterdam
PhD period:	2013-2016
Promotor:	Prof.dr. E.P. Prens
Supervisors:	Dr. H.H. van der Zee
	Dr. J. Boer

	Year	Workload (Hours/ECTS)
1. PhD training		
General courses		
- MolMed: Microsoft Excel 2010: Basic	2014	0.3 ECTS
- MolMed: Research management for PhD-students	2014	1 ECTS
- MolMed: Microsoft Excel 2010: Advanced	2014	0.4 ECTS
- MolMed: Photoshop and Illustrator CS6 for PhD-students	2014	0.3 ECTS
- Research Meetings, Department of Dermatology, Erasmus MC	2013-2016	50 Hours
Specific courses		
- MolMed: Basic human genetics course	2013	0.5 ECTS
- MolMed: Writing successful grant proposals	2013	0.5 ECTS
- MolMed: Basic introduction on SPSS	2013	1 ECTS
- MolMed: Biomedical English Writing Course	2014	2 ECTS
- Wetenschappelijke integriteit	2014	0.3 ECTS
- Basiscursus Regelgeving en Organisatie voor Klinische onderzoekers (BROK)	2014	1 ECTS
- Biomedical English Writing and Communication	2015	3 ECTS
Conferences and symposia		
- 3rd International Conference on HS research, Brussels, Belgium	2013	0.5 ECTS
- 2nd PhD weekend Dermatology, Erasmus MC, Maastricht, The Netherlands	2014	1 ECTS
- 4th International Conference on HS research, Brussels, Belgium	2014	0.5 ECTS
- 23th European Academy for Dermatology and Venerology (EADV) Conference, Amsterdam, The Netherlands	2014	1 ECTS
- Symposium on Autophagy in inflammatory diseases and cancer, Paris, France	2015	0.5 ECTS
- 3rd PhD weekend Dermatology, Erasmus MC, Wassenaar, The Netherlands	2015	1 ECTS
- 5th International Conference of the European Hidradenitis Suppurativa Foundation (EHSF), Berlin, Germany	2016	1 ECTS

	Year	Workload (Hours/ECTS)
Oral presentations		
- The clinical course of HS, Department of Dermatology, Erasmus MC, Rotterdam, The Netherlands	2013	0.5 ECTS
- Cohort vs case control studies, 2nd PhD weekend, Maastricht, The Netherlands	2013	0.5 ECTS
- Fumarates as a treatment option for HS, 3rd International Conference on HS research, Brussels, Belgium	2014	1 ECTS
- Hidradenitis suppurativa, 15th WCS congress, Utrecht, The Netherlands	2015	1 ECTS
- Severe hidradenitis suppurativa treated with wide excision, 5th International Conference of the EHSF, Berlin, Germany	2016	1 ECTS
- Hidradenitis suppurativa is associated with a low socioeconomic status, 5th International Conference of the EHSF, Berlin, Germany	2016	1 ECTS
Poster presentations		
- Fumarates as a treatment option for HS, 23rd EADV Congress, Amsterdam, The Netherlands	2014	1 ECTS
- Hidradenitis suppurativa: factors associated with disease severity, 23rd EADV Congress, Amsterdam, The Netherlands	2014	1 ECTS
Other		
- Mini symposium: B or T cells in auto-immune disease, Department of Immunology, Erasmus MC, Rotterdam	2014	4 Hours
- Workshop EndNote, Erasmus MC, Rotterdam	2014	6 Hours
- Reference meetings, 'Skintermezzo', Department of Dermatology, Erasmus MC, Rotterdam	2013-2015	1 ECTS
2. Teaching		
Supervising Master's thesis		
- Yalda Dahi	2014	1 ECTS
- Kelsey van Straalen	2015	1 ECTS
Supervising small research projects medical students		
- Dalibor Mihajlović	2014	0.5 ECTS
- Mustafa Erden	2015	0.5 ECTS
Occasional reviewer for the following journals		
- British Journal of Dermatology		
- Journal of American Academy of Dermatology		
- Journal of European Academy of Dermatology and Venereology		

CURRICULUM VITAE

Inge Elizabeth Deckers werd geboren op 30 november 1987 te Enschede. Op vijfjarige leeftijd verhuisde zij naar Hengelo waar ze haar verdere jeugd doorbracht. In 2006 behaalde zij haar VWO diploma aan de Vrijeschool 'de IJssel' te Zutphen. In datzelfde jaar werd zij ingeloot voor de studie Geneeskunde aan de Rijksuniversiteit Groningen. Nadat zij in 2009 haar bachelor behaalde, nam zij een korte pauze om vrijwilligerswerk te doen in Nepal, waarbij zij hielp met de opbouw van health-posts in het bergdistrict Dhading. In 2010 startte zij met de master Geneeskunde, waarbij zij haar junior coschappen liep in de regio Groningen en haar senior coschappen in het Deventer ziekenhuis. Het was in Deventer tijdens haar coschap dermatologie onder begeleiding van dr. J. Boer en dr. R. Houwing dat haar interesse voor het vak bevestigd werd en de interesse voor hidradenitis suppurativa geboren. Na het coschap sociale geneeskunde gevolgd te hebben aan de universiteit van Manipal in India, verhuisde zij in 2012 naar Rotterdam voor haar oudste coschap bij de afdeling Dermatologie van het Erasmus Medisch Centrum. Aansluitend deed zij op dezelfde afdeling haar keuzeonderzoek naar het klinisch beloop van hidradenitis suppurativa onder begeleiding van Prof.dr. E.P. Prens. Na het behalen van haar artsendiploma in 2013 kon zij haar onderzoek continueren als arts-onderzoeker onder begeleiding van haar promotor Prof.dr. E.P. Prens en haar copromotoren dr. H.H. van der Zee en dr. J. Boer. Naast haar promotie werkte zij mee aan meerdere klinische trials. Inge is op 5 juni 2015 getrouwd met Coen van Leeuwen met wie zij momenteel in Rotterdam woont. Binnenkort verhuist zij naar Groningen waar zij per 1 mei 2016 start met de opleiding Dermatologie in het Universitair Medisch Centrum Groningen.

DANKWOORD

Lieve collega's, familie en vrienden.

Het is gelukt, mijn proefschrift is klaar. Ik wil graag iedereen bedanken die me de afgelopen jaren geholpen heeft om dit proefschrift tot stand te brengen. Deze laatste pagina's wil ik graag gebruiken om een aantal mensen persoonlijk te bedanken.

Allereerst wil ik natuurlijk mijn promotor bedanken. Errol, vanaf het moment dat we elkaar hebben ontmoet, heb je je over mij ontfermd. Door jou ben ik enthousiast geworden over het doen van onderzoek. Je hebt uiteindelijk alles in het werk gesteld om mij te kunnen laten blijven als promovendus en daarvoor ben ik je eeuwig dankbaar. Dankzij jouw rustige uitstraling, je eeuwige enthousiasme en het vertrouwen wat je in me stelde, kon ik het beste uit mezelf halen tijdens dit promotietraject. Ik kon altijd bij je terecht, ook 's avonds en in het weekend. Dank je voor alles wat je voor me hebt gedaan de afgelopen jaren en ik ga onze samenwerking missen, hopelijk zien we elkaar nog vaak bij de HS research meetings.

Vervolgens wil ik mijn copromotoren Jurr en Hessel bedanken. Jurr, bij jou is mijn interesse voor HS begonnen als coassistent in Deventer. Tijdens mijn promotie was je altijd de rustige en stabiele factor, waarbij ik altijd terecht kon voor vragen en overleg. Hessel, je begon als mijn begeleider tijdens mijn oudste coschap en later werd je mijn copromotor. Dank je dat ik altijd bij je kon binnen lopen, en dat je al mijn stukken wilde lezen en herlezen. Ik hoop dat ik in de toekomst nog vaak met jullie kan samen werken.

Graag wil ik de leescommissie, dr. B. Horváth, Prof.dr. G.B.E. Jemec en Prof.dr. T. Nijsten bedanken voor het doornemen van het manuscript. Beste Barbara, daarnaast wil ik je bedanken voor de goede samenwerking de afgelopen jaren en voor het feit dat je meer in me zag en me de kans wil bieden om in Groningen de opleiding tot dermatoloog te volgen. Dear Gregor Jemec, thank you very much for being part of my inner committee. I would also like to thank you for all the projects that we have worked on together, and the valuable input you have given me during the past years. I hope we can continue this collaboration in the future. Beste Tamar, heel erg bedankt dat ik onderzoek mocht doen op de afdeling Dermatologie van het Erasmus MC en dat ik de laatste maanden mocht blijven als ANIOS. Daarnaast wil ik je bedanken voor alles wat ik van je heb mogen leren op het gebied van onderzoek.

Ik wil graag Prof.dr. M.F. Jonkman en Prof.dr. J.M.W. Hazes bedanken dat zij deel willen uitmaken van mijn grote commissie. Prof. Jonkman ik wil u verder bedanken voor uw vertrouwen in mij en dat u mij heeft aangenomen als AIOS in Groningen. Ik kijk erg uit om per 1 mei bij jullie op de afdeling te mogen starten.

Mijn lieve paranimfen, Sanne en Hester. Sanne jij was mijn eerste vriendinnetje hier in Rotterdam; we leerden elkaar kennen op de afdeling interne toen jij daar je coschap liep en ik mijn verdiepingsstage. Sindsdien hebben we vele avondjes samen doorgebracht en dankzij jouw onderzoeksachtergrond heb ik altijd met mijn onderzoeksperikelen bij je terecht gekund. Ik vind het ontzettend leuk dat jij nu ook gaat promoveren hier in het Erasmus, al had ik eigenlijk niets anders verwacht. Hester, als mijn buurvrouw aan het bureau op de derde heb ik je de afgelopen jaren steeds beter leren kennen. Dank je dat je altijd bereid bent geweest om mee te denken en antwoord te geven op mijn vele vraagjes. Daarnaast maak jij onderzoek doen gezellig!

Lieve Ingrid heel erg bedankt voor je hulp en gezelligheid bij de klinische trials. Jij hebt het mogelijk gemaakt dat ik deze trials naast mijn promotiewerk heb kunnen doen.

Beste Allard, als mijn opvolger als HS promovendus hebben we de laatste maanden veel samengewerkt. Dank je dat je mij een heleboel werk uit handen hebt genomen zodat ik me op mijn promotie heb kunnen focussen.

Ik wil graag de geneeskunde studenten bedanken die ik heb mogen begeleiden de afgelopen jaren. Kelsey van Straalen, Yalda Dahi en Dalibor Mihajlović, ik heb jullie stuk voor stuk zien groeien tijdens jullie wetenschapsstage en dankzij jullie zijn er een aantal prachtige artikelen tot stand gekomen.

Beste Caspar Looman en Loes Hollestein, heel erg bedankt voor jullie hulp bij de statistische analyses. Jullie hebben me menigmaal vooruit geholpen.

Beste Ronald Blokzijl, heel erg bedankt dat je me op weg hebt geholpen bij het CBS en dat je altijd de tijd hebt genomen om alle vragen die ik had te beantwoorden.

Beste Prof.dr. Hooikaas, heel erg bedankt dat ik bij de afdeling immunologie mocht starten met mijn promotie. Dankzij u was dit hele traject mogelijk.

Ik wil graag al mijn coauteurs bedanken voor de goede samenwerking. Dankzij jullie kritische blik en bijdrage is dit proefschrift tot stand gekomen.

Lieve Willeke, Tineke en Wendy, heel erg bedankt dat ik bij jullie heb mogen zitten op het secretariaat tijdens het begin van mijn onderzoekstijd. Jullie hebben me opgang geholpen en hebben voor een hele gezellig tijd gezorgd.

Lieve (oud)onderzoekers van de dermatologie, heel erg bedankt voor de gezellig tijd samen op de derma. Jullie stonden altijd klaar voor overleg en hielpen me menigmaal verder. Dankzij jullie was mijn promotietijd in het Erasmus niet alleen ontzettend leerzaam maar ook ontzettend leuk!

Beste ANIOS, AIOS en dermatologen van de afdeling dermatologie van het Erasmus MC, dank jullie dat ik de afgelopen jaren bij jullie werkzaam mocht zijn. Eerst als oudste co, daarna als promovendus en nu als ANIOS. Jullie stonden altijd open voor mijn vragen en ik heb enorm veel van jullie geleerd.

Ik wil graag mijn lieve familie bedanken die me geholpen heeft dit proefschrift te verbeteren. Thea en Elise, heel erg bedankt voor het doorlezen van de Nederlandse teksten uit mijn proefschrift. Dear Jane, thank you for carefully reading my discussion. Lieve Annelies, heel erg bedankt dat jij de voorkant van mijn proefschrift hebt gemaakt, wat is hij prachtig geworden!

Mijn lieve VIVA vriendinnetjes, Mandy, Alexandra, Sietske, Annemieke, Brigitte en Sandra, jullie hebben voor de gezelligheid gezorgd in Rotterdam. Bij jullie hoef ik even niet aan patiënten of promotie te denken. Ik ga de vele VIVA dates missen.

Lieve Mirjam, Nicole, Annemarije, Grytsje, Esther en Astrid, vanaf jaar 1 geneeskunde in Groningen zijn we vriendinnen. Alles hebben we samen doorlopen, de colleges in de blauwe zaal, de coschappen, het krijgen van onze eerste baan en ondertussen zijn we allemaal in opleiding. Tijdens onze vele weekendjes samen staan jullie altijd open voor mijn verhalen. Jullie zijn geweldige vriendinnen.

En natuurlijk wil ik mijn lieve ELO vriendinnetjes, Carmen, Minke en Pien hier noemen. Wat hebben we onder het genot van een wijntje aan lief en leed gedeeld over de afgelopen jaren. Jullie staan altijd voor me klaar en ik weet dat ik altijd bij jullie terecht kan. Jullie open en eerlijkheid maakt jullie de beste vriendinnen.

Mijn lieve schoonfamilie, het is niet in woorden uit te drukken hoeveel geluk ik heb gehad om jullie er als familie bij te krijgen. Vanaf het begin hebben jullie me opgenomen in jullie gezin. Jullie zijn altijd geïnteresseerd geweest in mijn promotie en hebben

geregeld met mij mee gedacht. Ik kijk er met veel plezier naar uit om binnenkort tante te worden van het nieuwste lid in de van Leeuwen familie.

Lieve papa en mama, jullie zijn geweldige ouders. Jullie staan altijd voor me klaar en hebben me altijd gesteund in mijn keuzes. Dankzij jullie eindeloze vertrouwen in mij, heb ik de dingen kunnen doen die ik graag wilde doen. Jullie zijn altijd geïnteresseerd geweest in wat ik aan het doen ben en het is heerlijk om ouders te hebben waarmee elk (medisch) onderwerp besproken kan worden aan tafel. Ook tijdens mijn promotie wilden jullie altijd graag horen wat ik aan het doen was en dachten mee met mijn onderzoeken. Lieve papa en mama, ik hou enorm veel van jullie.

Als laatste wil ik mijn lieve man Coen bedanken. Lief, dank je dat je er altijd voor me bent en voor me klaar staat, door jou kan ik het beste uit mezelf halen. Jij bent mijn rustige basis waar ik altijd bij thuis kan komen. Heel erg bedankt dat je ervoor gezorgd hebt dat ik me de laatste maanden volledig op mijn promotie heb kunnen richten, terwijl je zelf ook druk bent met je eigen promotietraject. Je hebt me door dalen geholpen en mee gefeest met de pieken. Je bent altijd bereid geweest om me te helpen, elke presentatie heb je gezien en je hebt bijna al mijn artikelen wel een keer doorgelezen en gecorrigeerd, waardoor je ondertussen ook behoorlijk wat van HS af weet. Verder wil ik je heel erg bedanken dat je zonder twijfel met me mee terug wilt verhuizen naar Groningen, zodat ik daar de opleiding kan volgen. De vanzelfsprekendheid waarmee je alles voor me doet is ongelofelijk bijzonder. Ik hou enorm veel van je, jij maakt mijn leven compleet.

Ik kan de hele wereld met één hand aan, als jij die andere maar vasthoudt

Financial support for the publication of this thesis was generously provided by:

AbbVie BV
Celgene BV
ChipSoft BV
Fagron BV
Janssen-Cilag BV
L'Oréal - La Roche Possay
Mediq i.s.m. Pierre Fabre Dermo-Cosmétique
Oldekamp Medisch BV
Pfizer BV
Tandartsenpraktijk van Leeuwen
Tobrix BV
Van der Bend BV
Will-Pharma

Stellingen behorend bij het proefschrift

Hidradenitis Suppurativa

Clinical Aspects, from Onset to Treatment

Inge Elizabeth Deckers

1. Prepubertal onset of hidradenitis suppurativa is not as rare as reported, and is associated with a family history of hidradenitis suppurativa and a more widespread disease.
   This thesis

2. Smoking cessation aids to remission in the course of years.
   This thesis

3. Inflammatory bowel disease, especially Crohn's disease, is more prevalent in patients with hidradenitis suppurativa.
   This thesis

4. The socioeconomic status of patients with hidradenitis suppurativa is significantly lower than of patients with other dermatological diseases.
   This thesis

5. Wide excision surgery is effective in severe hidradenitis suppurativa, leading to 50% remission/cure in an anatomical area.
   This thesis

6. A problem in the field of hidradenitis suppurativa that should be solved, is finding an appropriate replacement of the misnomers hidradenitis suppurativa, acne inversa, acne ectopica and Verneuil's disease.

7. Hidradenitis suppurativa: It looks infectious, but it is not.
   G.B.E. Jemec. Exp Dermatol, 2008

8. Anemia of chronic disease can be caused by failure of an increase in erythropoietin levels.
   Thesis of J.J. Bode, 1961

9. The assumption that your weight is based on genetics, leads to a higher body weight.
   M.C. Parent and J.L. Alquist. Health Educ Behav, 2015

10. Dyslexia also has its advantages, because dyslectic people are better at planning and keeping the overview.
    C. Leather et al. Dyslexia, 2011

11. Laissez lire, et laissez danser; ces deux amusements ne feront jamais de mal au monde.
    Voltaire, 1764

12. With a little bit of luck, good support and a lot of hard work, almost anything can be accomplished.
    This thesis