Comorbidities of hidradenitis suppurativa (acne inversa)

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Key words: hidradenitis suppurativa, acne inversa, autoimmune diseases, Crohn disease, spondylarthropathy, follicular occlusion, autoinflammatory disorders, Th17 cell cytokines

Abbreviations: ABD, Adamantiades-Behçet’s disease; CARD, caspase activation and recruitment domain-containing protein 15; CD, Crohn’s disease; CK, cytokeratin; HS, hidradenitis suppurativa; IL, interleukin; KID, keratitis-ichthyosis-deafness; NOD, nucleotide oligomerization domain; SAPHO, synoritis-acne-pushelosis-hyperosis-asteitis; SCC, squamous cell carcinoma; TNF, tumor necrosis factor

Comorbidities of hidradenitis suppurativa (acne inversa) were reviewed by extracting original and review publications included in MEDLINE, EMBASE and COCHRANE libraries using the terms “hidradenitis,” “Verneuil” and “acne inversa.” Follicular occlusion disorders, inflammatory bowel diseases, especially Crohn disease, spondylarthropathy, other hyperergic diseases, genetic keratin disorders associated with follicular occlusion and squamous cell carcinoma were the most common hidradenitis suppurativa comorbid diseases. A first classification of these major comorbidities and their possible genetic background reveals a list of chromosome loci and genes, which could be hidradenitis suppurativa candidates. Most of these diseases belong to the group of autoinflammatory disorders, where Th17 cell cytokines seem to play a central role.

Update on Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) or acne inversa is a chronic, inflammatory, recurrent, debilitating skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillaries, inguinal and anogenital regions (Dessau definition, 1st International Conference on Hidradenitis suppurativa, March 30-April 1, 2006, Dessau, Germany).³ It was first described in 1839 by Velpeau;² Verneuil⁴ gave it its name in 1854 and associated it with the sweat glands. Later, HS was classified as a member of the follicular occlusion triad, along with Acne conglobata and dissecting cellulitis of the scalp.²⁴ In 1975, pilonidal cyst was added as a member to this triad, forming the follicular occlusion tetrad.⁴ In 1989, Plewig and Steger introduced the term acne inversa to substitute the term HS.⁷ However, both terms, HS and acne inversa, are not proper denominations of the disease and do not represent its pathogenetic background.

HS is a disease of the terminal hair follicle associated with lympho-histiocytic inflammation, granulomatous reactions, sinus tracts and scarring.³⁵¹² The deep part of the follicle appears to be involved.¹²⁻¹⁶ A consistent finding in histological studies of HS is a follicular occlusion due to hyperkeratosis, regardless of disease duration, leading to occlusion of the apocrine gland with subsequent follicular rupture, inflammation and possible secondary infection. A reduction in the percentage of NK cells over time and a lower monocyte response to triggering by bacterial components was observed in patients with HS.¹⁷ Compared with normal skin, increased numbers of Toll-like receptor 2-expressing infiltrating macrophages (CD68⁺) and dermal dendocytes (CD209⁺) was detected in HS lesions.¹⁸ A perifollicular and subepidermal inflammation of CD3⁺, CD4⁺, CD68⁺, CD79⁺ and CD8⁺ cells, the latter with a striking selective epitheliotropism, could be detected in HS lesions.¹² Clinical improvement with the application of anti-inflammatory therapies, especially the combination of clindamycin with rifampicin and those targeted against the tumor necrosis factor (TNF)α and its receptor may be compatible with the above pathogenetic theory.¹⁵⁻²⁴

One of the most obvious hallmarks of the disease is the restriction to the skin areas affected. The disease is essentially limited to areas of the skin that are rich in terminal hair follicles and apocrine glands, such as the axilla, the anogenital area and mammary gland sites as well as the buttocks, nape of the neck and scalp (mostly at the inverse areas), although aberrant lesions may occur.²⁵⁻²⁶ Clinically, it is characterized by recurring pustules, inflammatory nodules, abscesses, draining sinus formation, fibrosis, secondary lymphedema and double-ended pseudo-comedones. HS is not acne; Closed comedones are not seen, since the deep part of the follicle appears to be involved and not its superficial compartment, as seen with acne affecting convex
HS inflammatory lesions are initially transient, but gradually become intransigent and associated with significant scarring. The diagnosis of HS is primarily made on the basis of its characteristic clinical presentation and has to meet the criteria adopted by the 2nd International Conference on Hidradenitis suppurativa, March 5, 2009, San Francisco, CA US (Table 1). The severity of the disease can be classified in three grades for each area involved according to the Hurley classification, a simple system that is, however, static and not suitable for a global assessment of severity. On the other hand, the Sartorius score and its modified versions can also be used to assess severity. It is a dynamic, global severity score, taking into account the extent of the disease and the number and severity of individual lesions. The Sartorius score yields a wide range of scores beginning at zero (inactive disease), with no upper limit.

After initial conflicting reports on HS epidemiology, reporting a varying prevalence of 0.3–4.1%, a global HS prevalence of 1% has been currently recorded in both a representative sample of the French population (n = 10,000) and in a review of several studies. A female predominance has been widely reported, of the male: female ratio is 1:2.7 to 1:3.3. Multivariate analysis showed a strong association with current smoking (odds ratio = 12.6, 95% CI 8.6–18.4) and body mass index (odds ratio = 1.1 (1.1–1.2)) for each increase of 1 U of Body Mass Index.

The inheritance mode of HS remains unclear. The group of experts, who participated at the 1st International Symposium has accepted that HS has to be a polygenic disease with sporadic cases having defects in a number of critical genes involved in its pathogenesis and familial cases with probably highly penetrant defect(s) in one of these genes. In some families, HS may show a single gene dominant inheritance. Fitzsimmons et al. studied three families with a total of 21 affected members and reported that the pattern of transmission and the number of affected individuals were consistent with an autosomal dominant inheritance. Later, they studied the families of 266 subjects with HS, comprising a total of 62 affected individuals. They reported that 34% were first-degree relatives in 11 families. Moreover, a history of disease in three generations in a patients’ family suggested an autosomal dominant inheritance. Genetic reports indicated several gene loci on chromosomes 6q25.1-25.2 and 9p12-p13.11, but no causative gene(s) have yet been identified. A genome-wide scan in a four-generation Chinese family identified a first locus for HS at chromosome 1p21.1–1q25.3 into a 76 Mb region flanked by the markers D1S248 and D1S2711.

### Associated Diseases and Possible Comorbidities

Hidradenitis has been associated with several endocrine disorders, such as diabetes, acromegaly and Cushing disease; however, no common pathogenetic background can be suggested. On the other hand, several, possibly associated diseases or groups of diseases have been reported in association with HS (Table 2). With the exception of the follicular occlusion triad, which seems to be closely associated with HS, however, without any current knowledge on common genetic etiology, the significance of the other comorbid conditions remains unknown. Interestingly, such associations include chronic, suppurative, hyperergic (positive pathergy skin reaction) disorders, such as inflammatory bowel diseases, especially Crohn disease, synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome, pyoderma gangraenosum, Adamantiaies-Behçet disease, spondylarthiritis without or with follicular occlusion triad signs, genetic keratin disorders associated with follicular occlusion, such as Pachyonychia congenita, and Down syndrome. At last the common development of epithelial tumors on HS lesions may be considered as the consequence of chronic severe inflammatory skin disease.

### Follicular occlusion tetrad

The disorders of follicular occlusion (Acne conglobata), dissecting cellulitis of the scalp and
pilonidal cyst) are well known associations with HS. A given patient may have two or more disorders within the tetrad. A past history of significant acne (long lasting, leaving scars) is recorded in 44% of males and 23% of females with HS. While dissecting folliculitis of the scalp is rare (1%), pilonidal cyst is frequently associated with HS, if both true sinus and midline intergluteal dimple are taken into account (30%).

Acne vulgaris is not associated with HS. Although in several studies 45, 50 and 70% of HS subjects, respectively were reported to have associated Acne vulgaris, current studies have shown that concomitant acne is not frequent in HS (20% in males, 10% in females) and that the prevalence of acne, hirsutism and irregular mensis are not more common in HS patients than in controls. Moreover, in contrast to the initial lesions of acne, no closed comedones are detectable in HS; the apparently open comedones are never closed; they are double-ended “pseudo-comedones,” i.e., literally scars. Elevated sebum excretion, which is a major pathophysiological feature of acne, is absent in HS.

Inflammatory bowel diseases: Crohn disease (CD) and ulcerative colitis. Several case reports and studies have suggested an association between CD and HS. In the largest of these reports, 24 of 61 (38%) HS patients also had a CD diagnosis. In most of these cases, CD only affected the large bowel, and its diagnosis preceded that of HS by 3.5 years; diagnosis of HS preceding that of CD has also been reported. It is postulated that the

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Table 2. Hidradenitis suppurativa and associated diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene map loci</th>
<th>Dysregulated genes</th>
<th>Encoding protein</th>
<th>Reported cases associated with HS</th>
<th>References</th>
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<tr>
<td>Inflammatory bowel diseases</td>
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<tr>
<td>(1) Crohn disease (CD), ulcerative colitis</td>
<td>16q12</td>
<td>NOD2/CARD15</td>
<td>caspase recruitment domain-containing protein</td>
<td>82</td>
<td>47–74</td>
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<td>(2) Crohn disease (CD) and squamous cell carcinoma (SCC)</td>
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<td></td>
<td></td>
<td>81</td>
<td>48–63</td>
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<td>SAPHO (synovitis, acne, palmoplantar pustulosis, hyperostosis, osteitis) syndrome</td>
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<td>Pyoderma gangrenosum</td>
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<td>9</td>
<td>75–77</td>
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<td>Adamantiades-Beḥçet disease (ABD)</td>
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<td>7</td>
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<td>Spondylarthropathy SPDA1 SPDA2</td>
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<td>80–84</td>
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<td>(1) without additional signs</td>
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<td>(2) with acne conglobata or follicular occlusion triad (HS, acne conglobata, dissecting cellulites of the scalp)</td>
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<td>Genetic keratin disorders associated with follicular occlusion</td>
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<td>(1) Pachyonychia congenita (PC-2)</td>
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<td>(2) Dowling-Degos disease</td>
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<td>(a) without additional signs</td>
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<td>(b) with arthritis</td>
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<td>(c) with squamous cell carcinoma (SCC)</td>
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<td>Other genetic disorders</td>
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<td>(1) Keratitis-ichthyosis-deafness (KID) syndrome</td>
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<td>(2) Down’s syndrome</td>
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<td>Epithelial tumors*</td>
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<td>(1) squamous cell carcinoma (SCC)*</td>
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<td>(2) adenocarcinoma*</td>
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*SCC and adenocarcinoma have to be considered as a consequence of chronic inflammation and not as a real comorbidity.
local swelling and inflammation associated with CD may precipitate the development of perianal HS in patients already prone to this pathology. Cutaneous CD mimicking HS has to be taken into consideration in case of sole perianal lesions. Metastatic CD cannot be easily differentiated from HS, however, the concept of autointoxication—HS may result from absorption of toxins from the bowel—may indicate that metastatic CD is actually HS. Minor defects of intestinal mucosal barrier function may result in failure of intestinal IgA to inactivate bacterial and dietary antigens. The IgA immune complexes formed are deposited in the skin. Evidence for this theory includes the presence of IgA immune complexes in dermatitis herpetiformis. Therefore, HS may also be the result of abnormal host-microbial interactions involving pattern recognition receptors such as toll-like receptors and nucleotide oligomerization domain (NOD).

The caspase activation and recruitment domain-containing protein (CARD) 15, which corresponds to the IBD1 locus mapped on chromosome 16q12, is the first identified non-HLA gene related with CD. CD-associated mutations are localized in the leucin rich repeats domain and cause loss of function of NOD2, reducing sensing of muramyl dipeptide, the NOD2 agonist and inducing NFκB signalling. Therefore, CARD15 mutation-associated CD may be caused by immunodeficiency for enterobacteria, such as Mycobacterium avium paratuberculosis. Nevertheless, because gene targeting experiments showed conflicting results, the role of CARD15 mutations in CD is still unclear. NOD2 deficiency rather upregulates Toll-Like Receptor 2 responses and increases susceptibility to bacterial antigen-specific T-helper 1-type colitis, thus providing an appropriate model of human CD. However, a pilot study carried on 10 HS patients detected no CARD15/NOD2 polymorphisms.

Synovitis, acne, SAPHO syndrome, pyoderma gangraenosum, ABD. SAPHO syndrome is characterized by arthritis and/or osteitis with preferential anterior chest wall involvement, and although most commonly associated with palmoplantar pustulosis, it has also been associated with other chronic suppurative skin disorders including HS, Acne conglobata or Acne fulminans, and dissecting cellulitis of the scalp. The association of pyoderma gangraenosum with several systemic disorders is well established. In a review of 86 patients with pyoderma gangraenosum, arthritis was present in 37% of patients and inflammatory bowel disease in 36%, while 10% had a monoclonal gammopathy and 5% (four patients) had associated HS. The pathogenesis of pyoderma gangraenosum is unknown, although numerous defects of the immune system have been implicated including defective neutrophil chemotaxis and phagocytosis, reduced lymphokine production and migration. A suggested common link for HS and pyoderma gangraenosum is a defective neutrophil function, which has been discussed in the literature.

ABD is a chronic, systemic, inflammatory, vascular disorder of unknown aetiology, characterized by recurrent oral aphthosis, genital ulcers, uveitis and skin lesions. Genetic factors have been investigated, and a link with with HLA-B51 has been suggested, however, HLA-B51 represents a prognostic marker rather than an etiologic factor. A HLA-independent higher frequency of IL-12B promoter polymorphism in ABD patients than in controls has also been described. HS is one of the less commonly appreciated complications. In vitro and in vivo studies have shown that overactive neutrophils play a key role in the pathophysiology of ABD. The enhanced expression of adhesion molecules may be responsible for the tissue neutrophilia and may induce the dense infiltrate surrounding the sweat glands and/or hair follicles in patients with ABD.

Spondyloarthropathy. Spondyloarthropathy, one of the commonest chronic rheumatic diseases, includes a spectrum of related disorders comprising the prototype ankylosing spondylitis, a subset of psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated spondyloarthropathy. HLA-B27 predisposes to all phenotypic subsets, which are considered as various phenotypic expressions of the same disease. An additional susceptibility locus has been identified on 9q31-q34 (SPDA2).

The association of HS with inflammatory, peripheral oligoarthritis and seronegative spondyloarthropathy has been reported. It is hypothesized that the arthropathy may represent a reaction to chronic skin infection. There is a close association between flares of HS and exacerbation as well as severity of arthritis. Conversely, improvement of arthritis follows surgical therapy for HS.

There are fewer reports of seronegative arthritis associated with the follicular occlusion triad than arthritis associated with HS. Clinical findings include a chronic course with episodic inflammatory oligoarthritis and/or axial arthritis. Characteristic laboratory findings include anaemia of chronic disease, elevated erythrocyte sedimentation rate and negative rheumatoid factor. There is no increased incidence of HLA-B27 or other HLA-B alleles in contrast with other seronegative spondyloarthropathies. A follow-up study of 44 patients with HS and/or Acne conglobata confirmed this distinctive arthropathy, demonstrating a peripheral inflammatory arthropathy in 29%, an axial arthropathy in 14% or a combination of both in 57%. Rosner et al. and Bhalla and Sequeira reported that the axial skeleton is not invariably involved and even when affected may be asymptomatic. Expression of multiple HLA-B and -DRW4 in patients with HS and spondylarthropathy and elevation of circulating immune complexes suggest that immunogenetic mechanisms may play a role in the concomitant manifestation of these diseases, although Lapins et al. reported no HLA association in Swedish patients with HS.

Genetic keratin disorders associated with follicular occlusion. Pachyonychia congenita is a group of autosomal dominant ectodermal dysplasias in which the main phenotypic characteristic is hypertrophic nail dystrophy. In the Jackson-Lawler form (PC-2), pachyonychia is accompanied by multiple pilosebaceous cysts, nasal teeth and hair abnormalities. Heterozygous missense mutations in keratin 17 and/or keratin 6b genes cause either PC-2 or a phenotype resembling steatocystoma multiplex. Several cases have been described in which the patients with PC-2 also have varying degrees of HS.
Pitted scars. The disorder is caused by loss-of-function mutation in the keratin 5 gene. A single underlying defect in follicular epithelial proliferation, characterized by variable expressivity, may account for the coexistence of the clinically distinct disorders of follicular derivation Dowling-Degos disease and HS.\(^{100,104}\)

**Other genetic disorders.** Keratitis-ichthyosis-deafness (KID) syndrome is a rare congenital disorder of the ectoderm caused by mutations in the connexin-26 (GJB2) on chromosome 13q11-q12, giving rise to keratitis, erythrokeratodermia and neurosensory deafness. Four cases of KID syndrome occurring in association with follicular occlusion triad have been reported.\(^{108-110}\) This unusual phenotype is associated with a novel heterozygous point mutation (C119T) in the gap junction protein, which substitutes a valine for alanine at codon 40 (A40V) in the connexin 26 protein. Through Xenopus oocyte expression studies, this mutant protein was shown to significantly disrupt the function of the specialized gap junctions connecting the cytoplasm of adjacent cells critical for tissue homeostasis. Mutations within the connexin 26 protein are associated with syndromes involving both sensorineural deafness and hyperkeratotic skin disorders.

**Squamous cell carcinoma (SCC), adenocarcinoma.** SCC can be considered as the most severe complication of HS; however, its common occurrence in HS may indicate comorbidity.\(^{143}\) HS transformation into SCC has been reported 41 times.\(^{74,106,107,112-117}\) The HS/SCC male: female ratio is 4:1, most SCC (61%) present at the perineal or buttock area. The presence of HS prior to SCC diagnosis ranges from 3–50 years with a mean of 25 years. Age at diagnosis of SCC ranges from 27 to 71 years, and 15 of the patients (48%) in a study died within 2 years of SCC diagnosis.\(^{112,113}\)

Kurokawa et al.\(^{114}\) studied the cytokeratin (CK) expression in two cases of well-differentiated and poorly differentiated SCC arising from HS. In tumor nests of well-differentiated SCC, CK1 and 10 expressions were downregulated, and CK14 expression was upregulated. In tumor nests of poorly differentiated SCC, CK1 and 10 were not expressed but simple epithelial keratins (CK8, 18 and 19) were expressed. These changes of CK expression are related to malignant transformation from the sinus tract (type A epithelium) in HS to SCC.

Baresi et al.\(^{115}\) reported on a HS case complicated by SCC in association with a rare tumor, a diffuse malignant peritoneal mesothelioma arising in the absence of predisposing factors. Interestingly, frequent losses in chromosomal region 1p.21-22 have been found in mesothelioma, a region in which a possible locus for HS was found in Chinese family.\(^{19}\)

**Conclusions and Perspective**

Two major groups of disorders are possibly comorbid with HS, namely chronic hyperergic inflammatory diseases and acquired and inherited follicular occlusion disorders. Interestingly, the reported inflammatory diseases and acquired follicular occlusion disorders have been previously associated with autoimmune phenomena, while currently with hyperactive neutrophils implicating neutrophil dysfunction.\(^{144}\) Recently, a group of autoinflammatory disorders has been identified characterized by recurrent non-infectious inflammatory episodes in the absence of pathogens, autoantibodies or antigen-specific T cells.\(^{145}\) These disorders are caused by primary dysfunction of the innate immune system, without evidence of adaptive immune dysregulation. Innate immune abnormalities include aberrant responses to pathogen associated molecular patterns, prominent neutrophilia in blood and tissues, and dysregulation of Caspase 1-induced proteolytic activation of inactive precursors of interleukin (IL)-1 cytokine family, such as IL-1β, IL-18 und IL-1F7b or of their receptors. There are a few genes, which have been associated with different groups of autoinflammatory disorders and NOD2 mutations have been commonly accused for CD, pyoderma gangraenosum and SAPHO syndrome.\(^{146}\) ABD and spondylarthropathy have also been classified to the autoinflammatory disorders by some authors.\(^{147}\) NOD2 has been reported to bridge innate immunity and autoinflammation.\(^{148}\) Mutation in the inflammasome/NOD signalosome have been shown to cause inflammasome hyperactivation, which potentiates Th17 cell-dominant immune responses and increase of the Th17 cell-related cytokines and factors such as IL-17a, IL-17f, IL-23p19, IL-23 receptor, RORγt and IL-22 in mouse skin.\(^{149}\)

In strict sense, autoinflammatory disorders are caused by mutations of pattern-recognition receptors and perturbations of the cytokine balance.\(^{150}\) Recent expansion of identified genes responsible for various autoinflammatory disorders has dramatically improved the understanding of innate immune signaling pathway, especially the signaling mediated by the CARD family of proteins, thought to be active in apoptotic and inflammatory signaling pathways.\(^{151}\) Veillette et al.\(^{152}\) suggested the family of protein tyrosine phosphatases as negative regulators of inflammation. TNF receptor superfamilies are intimately involved in innate immunity. This gene is critical for limiting inflammation by terminating TNF-induced NFkappaB responses. The clinical improvement of HS with anti-TNFα therapies supports the hypothesis for an altered immune response in this patients.\(^{21}\) A reduction in the percentage of natural killer cells over time and a lower monocyte response to triggering by bacterial components is observed in patients with HS.\(^{17}\) IL-17, the signature cytokine of Th17 cells, has been implicated in the pathogenesis of rheumatoid arthritis and CD.\(^{153}\) Since Th17 cell cytokines play a central role in mediating mucosal immunity to gastrointestinal pathogens, the role of the Th17 cell-related cytokines in the pathogenesis and treatment of HS has to be investigated.


14. Pilbrum DM, Shelley WB, Kligman AM. Bacterial infec-


23. Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa and familial benign pem-


29. Jemec GB, Heidemink M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential pre-


