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Current Status of Hidradenitis Suppurativa

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Abstract

Background: Hidradenitis suppurativa (HS), known as acne inversa, is a relapsing and chronic inflammatory skin disease affecting the skin folds. Scarring and infection are the most common complications that also cause a significant morbidity and impair the quality of life of these patients. Local complications of the disease include the development of strictures in the local scars, anus, urethra or rectum, which may result in limitation of movement; genital edema that may cause functional impairment. All wounds that can not complete the natural healing process have potential for developing dysplastic changes. There is also a risk of developing squamous cell carcinoma in HS patients with refractory disease with prolonged courses. Treatment depends on the stage, frequency of exacerbation and the goal of the patient. Tobacco cessation, weight reduction, control of cardiovascular risk factors, avoidance of the use of irritants in affected areas, hair removal using lasers are elementary precautions which can be taken. Unfortunately, HS one single treatment modality that has sufficient efficacy or treatment modality. Today, systemic agents including oral antibiotics, retinoids, androgens and biological agent, surgical procedures and lasers are used in the management of HS. In this review, clinical findings along with accompanying diseases and treatments are discussed, in the light of the current literature

Introduction

Hidradenitis suppurativa (HS) has been defined as a recurrent, debilitating chronic inflammatory disease which is characterized by painful, deep-seated, rounded nodules and abcesses of apocrine gland bearing skin and in which subsequently sinus tracts and hypertrophic scarring occurs [1]. HS is historically referred to *Verneuil* disease, a French surgeon who associated the disorder with apocrine glands in the mid 19th century and named the disease as "hidradenitis suppurativa" [2]. In later years, follicular occlusion was thought to be the primary event in HS, and the condition was consequently included in the follicular occlusion triad, together with acne conglobata and dissecting cellulitis. Subsequently, with the addition of a fourth condition, pilonidal sinus, the triad became a tetrad and acne inversa was used as an alternative name of the disease [3].

The follicular occlusion which is thought to be responsible for etiopathogenesis of HS is caused by infundibular keratosis and hyperplasia of the follicular epithelium and results in accumulation of cellular debris and eventually cyst formation. When the hair follicle ruptures, a massive local immune response arises which results in painful abscess formation and afterwards sinus tract formation

and scarring. Although HS is characterized by suppuration, it is not generally triggered by infection and does not originate in apocrine sweat glands. It is proven that the sweat glands are not primarily or selectively inflamed. For this reason the term HS is not accurate and is accepted as a misnomer [**4**].

Epidemiology

HS typically occurs after puberty, with average age of onset in the second or third decades of life. The disease tends to be active during the third and fourth decades of life while it tends to improve after menapause. Patients over the fifth decades of life with active disease are typically men [**1,5**]. The prevalance of HS varies widely in previous studies. Several studies reviewed by Martorell indicate prevalence rates between 1%-4% in the general population [**5**]. HS is significantly more common in females than males with a defined ratio of 3.3 to 1 [**6**].

Etiology

The etiology of the disease is not fully known. About 30%-40% of the patients with HS have a family history of the disease. HS appears to be a genetically heterogeneous disease with several mutations at various locations [**6**]. Mutations that inactivate the presenilin 1 gene (PSEN1), presenilin enhancer gamma secretase subunit gene (PSE-NEN) and the nicastrin gene (NCSTN) have been described in families with severe and atypical clinical forms of HS [**5**]. Notch, an integral membrane protein plays a significant role in no rmal hair follicle development. Notch signalling suppresses Toll-like receptor-4 related proinflammatory cytokine responses via macrophages [**7**]. Inherited or acquired impairment of Notch signalling may play a key role in the development of HS [**4**].

Smoking, obesity and mechanical forces, hormones are well-known associated risk factors for HS. The chemical components in tobacco activate keratinocytes, fibroblasts and immunocytes. Smoking also induces proinflammatory cytokines like TNF-α, IL-1a, 1b, IL-8 which leads to neutrophil chemotaxis and TH17 cell induction [**4**]. Obesity may aggravate HS due to increased skin-skin and skin-clothing friction [1]. Rates of obesity in HS range from 12% to 88% which depends on the population [**8**]. In a retrospective study in which it was aimed to investigate if there was an association between HS and metabolic syndrome, 366 patients who had diagnosis of HS were matched with a control population of 366 subjects. Of the 243 patients with HS and 222 control subjects who had enough data to determine the presence of metabolic syndrom (having 3 or more of obesity, hypertriglyceridemia, low HDL, diabetes mellitus and hypertension), the prevalence of metabolic syndrome in patients with HS was 50.6%, which was significantly higher than the control group [**9**]. It was also found that smoking and obesity affect the clinical course in HS. In a study of 212 patients with HS whose median follow-up period was 22 years, a survey was conducted which revealed that smoking and obesity were significantly associated with lower rates of remission and poor prognosis [**10**].

Premenstrual flare-ups, female dominance, frequent occurence after menarche, improvement during pregnancy and menopause indicate the role of hormonal factors and suggest the hyperandrogenic situations. However, the general absence of clinical signs of hyperandrogenism, the normality of circulating androgens, the absence of hyperseborrhea and limited effects of anti-androgen treatments rule out the key role of hyperandrogenism [**6**].

In a retrospective case-control study which included 1776 patients of an appropriate HS diagnosis, it was found that HS was signif icantly associated with smoking, arthro pa thies, dyslipidemia, polycystic ovarian syndrome, psychiatric disorders,obesity, drug dependence, hypertension, diabetes, thyroid disease, alcohol dependence, and lymphoma when compared with control group. For this reason a multidisciplinary approach to hidradenitis suppurativa is recommended [**11**].

The spectrum of cytokines in the skin with HS was compared with normal appearing perilesional skin and the skin of healthy donors. IL-1B, TNF-α and IL-10 were significantly elevated in HS skin and perilesional skin when compared with the skin of healthy donors, providing evidence for the use of anti TNF-α biologics in HS. In that study it was also found that the levels of IL-1B, TNF- α and IL-10 levels tended to be correlated with disease severity [**12**].

Clinical Findings

The disease is located in the intertriginous regions of the apocrine sweat glands. The most common areas of involvement are axillary, inguinal and perineal regions, as well as the perianal region, the inner surface of the thighs, the submandibular region and the genital region are also involved. Pruritus and tenderness develop early in the lesion area. Subsequently, painful induration of the papules and subsequent deep subcutaneous nodules develop. These nodules quickly become drained and a malodorous discharge begins. The lesion is painful, erythematous nodule. The lesion, which does not show pustular formation, opens within a few days and the purulent material flows and heals with fibrosis. In these scarred areas, the disease often causes deep cavities and tunnels during the course of the disease. After each new lesion, the resulting scar and sinus areas begin to unite. Recurrent disease processes eventually result in fibrosis areas joining together to form bands that cause large interrelated contractions. The disease affects the quality of life of the patients to a great extent. Both malodorous discharge and pain cause the quality of life of the patients to deteriorate at an advanced level [**3, 4, 5, 6, 7, 8, 9**].

Local complications of the disease include the development of strictures in the local scars, anus, urethra or rectum, which may result in limitation of movement; genital edema that may cause functional impairment. All wounds that can not complete the natural healing process have potential for developing dysplastic changes. There is also a risk of developing squamous cell carcinoma in HS patients with refractory disease with prolonged courses. There is also the risk of developing amylodiosis in such cases. Untreated cases can cause systemic infection and cause septicemia [**9, 10, 11, 12, 13**].

HS is mainly clinically diagnosed. Chronic recurrent course and healing resulting to scarring in patients with typical skin lesions are also considered valuable in terms of diagnosis and treatment plan.

One of the first severity grading systems for HS was proposed by Hurley. It is substantially based on the presence and extent of cicatrization and sinuses. Its advantage is its simplicity [**14**]. Sartorius et al have suggested a more sophisticated scoring system including the involved anatomic regions, number and types of lesions, distance between lesions and the presence of normal skin in between lesions [**15**].

Treatment

Treatment depends on the stage, frequency of exacerbation and the goal of the patient [**6**]. Tobacco cessation, weight reduction, control of cardiovascular risk factors, avoidance of the use of irritants in affected areas, hair removal using lasers are elementary precautions which can be taken [**16**].

Topical Treatment

Long term efficacy data are limited for topical treatments for HS. The use of antiseptics and topical antibacterial agents may decrease the bacterial colonization. Bacteria are thought to contribute to the pathogenesis of HS. The microbiome of HS, however, is complicated by the fact that cultures from the lesions are frequently sterile. In addition, antibiotics do not play a curative role in the management of HS. Howevever topical clindamycin is suggested as first-line therapy for patients with Hurley stage I HS [**17**]. In a study of 27 HS patients who used topical clindamycin 1% solution twice daily for 12 weeks, it was found effective in abcesses and pustules, but not inflammatory nodules [**18**]. In addition, although not studied in RCTs, topical resorcinol and topical retinoids also have been useful in limited cases [**17**].

One of the most widely used local treatment in HS is intralesional corticosteroids. Triamcinolone acetonide injections are effective in the remission of inflammatory nodules within 48-72 hours in patients with acute local lesions [**16**].

Systemic Treatment

LFirst-line treatments for HS are treatments supported by high levels of evidence and favorable results. First line systemic treatments are combination of oral clindamycin and oral rifampicin, oral acitretin, dapsone and biological therapies of adalimumab and infliximab (**Table 1**) [**16**].

Oral antibiotics: The combined use of clindamycin 300 mg twice daily and rifampicin 300 mg twice daily for 10 weeks is one of the most common treatments used to induce re-

mission in every stage of patients (Hurley Stage 1,2 or 3) [**16**]. A complete remission, sometimes lasting for a year is provided in some patients [**6**]. In less severely affected patients or after the 10 weeks of clindamycin-rifampicin, when inflammation is reduced, long term administration of oral tetracycline may be helpful [**6**]. Besides their antibacterial properties, tetracyclines have an anti-inflammatory effect that is not fully understood [**19**]. It is hypothesized that tetracyclines may block TNF-α, through inhibiting TNF-α converting enzyme [**20**].

Dapsone: In a retrospective study of 5 patients treated with dapsone, improvement was reported in all of the patients in the first 4-12 weeks of the therapy at doses ranging from 25-150 mg/daily. In the median follow up period of 24 months, all patients required a maintenance therapy of 50-150 mg/daily doses. In that study it is hypothesized that dapsone has an impact on HS similar to other inflammatory dermatoses.(i.e. inhibits neutrophil chemotaxis) [**21**].

Acitretin: In a prospective study of HS, 17 patients were treated with 0.5-0.6 mg/kg daily doses of acitretin for 9 months. Improvement in condition generally started within the first 3 months of therapy and further improvement was achieved throughout the next few months. Therefore the cessation of the treatment is suggested if there is no satisfactory improvement after 3 months. In that study, it was highlighted that although acitretin was a promising treatment in HS, fast relapses occured in discontinuation of the treatment [**22**].

In another retrospective study including 12 HS patients of Hurley stage 2-3, all of the patients showed significant improvement during the treatment which lasted for 9-12 months. Contrarily, another oral retinoid, isotretinoin (the gold standart therapy for acne vulgaris) has not proven to be effective in HS which strongly indicates that the analogy between acne and HS is limited [**23**].

Infliximab: In a study, 10 patients with severe recalcitrant HS were treated with infliximab 5 mg/kg for a single course (only 3 infusions at weeks 0, 2, 6). All patients improved within 2-6 weeks. After a month, the mean CRP was reduced 31.7 to 5.5 mg/mL-1 while ESR was reduced from 31.8 to 11.5. In 3 patients, long lasting improvement was observed with no recurrence of lesions in 2 year follow up. 7 patients showed recurrence after a median time of 8.5 months. (range: 4.3-13.4 months) One of the problems with long-term treatment is the possible development of antibodies against infliximab. In patients with psoriasis or rheumatoid arthritis, combination with low dose methotrexate may inhibit antibody formation. But in hidradenitis suppurativa patients, it would be uncommon to prescribe methotrexate, because methotrexate is not an effective treatment option for hidradenitis [**19**]. In another study 11 patients with severe HS were reported who received infliximab 5 mg/kg every 4 weeks with a median follow up of 60.3 months. In 9 patients the disease was well controlled on this regimen. However, the patients experienced secondary infections of HS

Table 1. Systemic/Biologic Therapies in Hidradenitis Suppurativa [**16**]

Systemic/Biologic Therapies	
First line systemic/biologic therapies	Clindamycin+Rifampicin Oral acitretin Dapsone Adalimumab Infliximab
Second line systemic/biologic therapies	Hormone therapy Systemic corticosteroids Cyclosporine Methotrexate Alitretinoin Metformin Anakinra/ Canakinumab Ustekinumab

lesions, respiratory tract infections and minor weight gain (a median of 2.2 kg) [**24**].

Adalimumab: Superiority of weekly adalimumab dosing in HS over the fortnightly dosing regimen has been demonstrated in a randomized controlled study [**25**]. A prospective, randomized, double blinded, placebo controlled study was performed to test the efficacy of adalimumab in HS, in which 21 HS patients with Hurley stage II or III were included. Actively treated patients (n=15) received adalimumab 80 mg at baseline followed by 40 mg s.c. every other week for 12 weeks while the other group (n=6) received placebo. After 6 weeks a significant reduction in HS severity was gained in the treatment group but after 12 weeks, as for the disease severity scores, difference between treatment group and placebo group was not statistically significant. All patients relapsed 3 months after the treatment which suggested suppressive rather than curative treatment for adalimumab [**26**].

Etanercept: In a prospective open-label phase II study, etanercept was administered 50 mg once weekly for 12 weeks in 10 patients with HS and they were followed up to 24 weeks. At weeks 12 and 24, > 50% improvement in Sartorius score was observed in 6 and 7 patients respectively. But when the treatment was stopped, drainage of pus from affected areas recurred in 8 patients. Results of that study suggested that etanercept was a safe and effective therapy for hidradenitis suppurativa [**27**].

Ustekinumab: Ustekinumab is a human IgG1K monoclonal antibody that binds with high affinity to the p40 subunit of IL-12 and IL-23. In an open-label, prospective study, the efficacy and safety of ustekinumab has been investigated in a group of 17 patients with moderate- to-severe HS. Subcutaneous injections were administered at weeks 0 and 4 (induction phase) and 12 weekly thereafter (maintenance phase). Each injection contained 45 mg ustekinumab, with participants weighing >100 kg receiving 90 mg per injection. The intervention period was set to 40 weeks, consisting of the treatment phase (weeks 0–28) followed by a post-treatment phase of 12 weeks. At every visit, the modified Sartorius scale (mSS) which involved anatomical regions, the type and number of lesions, the extent of involvement and Hurley stage was assessed. Moderate-to-marked improvement of the modified Sartorius score was achieved in 82% of patients at week 40. In that study, low leukotriene A4-hydrolase levels was correlated with good response to ustekinumab [**28**].

Switch of biological agents: In a retrospective study of 19 HS patients who were treated with biological drugs, the first biological agent was adalimumab in 9 patients, infliximab in 7 patients, ustekinumab in 2 patients and etanercept in 1 patient. The mean duration of biological treatment was 12 months. (4-32 months) A complete response was observed in 3 patients (2 patients treated with infliximab and one treated with ustekinumab). 10 patients achieved a partial improvement while in 4 patients there was no clinical improvement and a worsening of the skin lesions was observed in one patient. One patient presented a severe infusional reaction while taking infliximab and the therapy was ceased. Treatment withdrawal were due to severe side effects or inefficacy in a total of 8 patients. Because of inefficacy, 6 patients switched to a second biological treatment: 3 patients to adalimumab (2 patients from infliximab, 1 from etanercept). Of these 6 patients, 3 achieved partial response, 3 showed no clinical response. Two patients switched to a third biological drug (1 adalimumab, 1 infliximab). In both cases partial improvement was seen. In that study the used dosage was the doses recommended by European Guidelines for Psoriasis. The best biological drug and its dosage for the treatment of HS are not known. Studies comparing biological drugs for HS are lacking but it seems that etanercept would be less effective. In that study also the only patient who received etanercept did not improve. It was concluded that biological treatments were an effective therapeutic option for severe cases of HS, but complete response was uncommon and partial responses were frequent [**29**].

Cyclosporine: A case was reported who was recalcitrant to several antibiotic therapies, oral isotretinoin, infliximab (5mg/kg- 4 infusions), etanercept (2x25 mg/week) to whom cyclosporine-A 5mg/kg/day was started finally. After two months a remarkable improvement of lesions was observed and the dosage was reduced to 3 mg/kg/day which

continued to the end of two years proving the efficacy of cyclosporine-A. The use of cyclosporine-A in HS has rarely been reported in the literature; in the few cases documented, it has been shown to be effective and well tolerated [**30**].

Antiandrogen therapy: Several trials using antiandrogen therapy have been conducted. In a randomized trial comparing ethinyloestradiol 50 mg/cyproterone acetate 50 mg with ethinyloestradiol 50 mg/norgestrel 500 mg in 24 patients, both regimens produced improvement in disease activity. 7 patients achieved long term (18 months) clearence of their lesions [**31**].

In a study, 7 patients with HS used finasteride 5 mg/daily (a type II 5α reductase inhibitor). All patients improved, in 3 patients complete healing of the lesions occured and 2 of the patients experienced a disease remission for 8-18 months [**32**].

Metformin is a hypoglycemic medication which also has antiandrogenic effect by increasing insulin sensitivity. In a study of 25 patients with HS, patients were treated with metformin and 75% achieved improvement to some extent in HS severity scores [**33**].

A systematic review of all of the systemic therapies: In a systematic review of 87 studies (comprising a total of 518 patients who received systemic immunosuppressive agents or systemic retinoids) which was published in 2013, it was determined that highest response rates were observed with infliximab, adalimumab and (with a lower quality of evidence) acitretin. However it was declared that the quality of evidence was low which made the direct comparisons difficult. The immunosuppressive therapies evaluated in these papers were biologics [adalimumab (15 studies, n=68), infliximab (42 studies, n=147), etanercept (9 studies, n=54), ustekinumab (2 st udies, n=4)], colchicine, ciclosporin, methotrexate and dapsone]. Treatment with systemic retinoids included the use of acitretin and isotretinoin. In that systematic review, there were 7 studies which evaluated the effects of oral isotretinoin comprising 174 patients and it was found that only 32 patients (18%) showed significant improvement. In the 6 studies with a total of 22 patients who received etretinate or acitretin (which is a metabolite of e tretinate); 16 patients (73%) showed significant improvement [**34**].

Surgical Treatment

Surgical removal of the actively inflamed area in hidradenitis suppurativa is often curative. [**35, 36**]. Surgery must fulfil the following 3 principles in HS: 1-Epithelialized sinus tracts and the associated keratinous debris must be unroofed, traced and removed to eliminate the materials acting as foreign bodies under the skin. 2-Seropurulent inflammatory material must be drained and completely removed, and cultures must be obtained if there is doubt for infection. 3-The invasive proliferative gelatinous mass requires careful identification, accurate tracing, and full eradication. Before surgery, medical agents should be used to soothe tissue inflammation which allow easier distinction between the involved tissue and normal tissue and prepare the wound for optimal healing.

Several surgical techniques are indicated for HS are: 1- local destruction 2- incision and drainage 3- mini-unroofing by punch debridement 4- mini-unroofing by standard unroofing (deroofing) to all involved margins 5-surgical excision beyond all clinically apparent margins [**34**].

Laser and Light Based Treatment Options

In recent years, laser and light based therapies are increasingly used in the management of HS. These adjuntive therapies act in reducing the frequency of painful flares in two ways. 1) By decreasing the number of hair follicles, sebaceous glands and bacteria in affected areas. 2) By ablatively debulking chronic lesions. To reach the hair bulb and minimize the possible damage to epidermal basal layer, devices with longer wavelengths are are preferred. 1064-nm NdYag laser has been studied most extensively. Tissue debulking with CO2 laser has been desribed as an effective alternative treatment of HS [**37**].

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