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Hidradenitis Suppurativa

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Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by the formation of nodules, abscesses, and fistulae at intertriginous sites. Pain, pruritus, malodor, and suppuration have a significant impact on quality of life for HS patients. Prevalence figures vary greatly in the literature from 0.05% to 4.1%, and HS is more common in females. The current understanding of the etiology and pathogenesis of HS is incomplete; numerous hypotheses concern the interplay of lifestyle factors, skin microbiota, genetics, and a dysregulated immune system. Due to its phenotypic heterogeneity and multifactorial pathogenesis, HS is a complex disease that can prove challenging to manage. Two approved biologic therapies for the management of HS have led to clinical response in approximately 50% of treated patients. New therapies targeting the interleukin (IL)-1, IL-17, IL-36, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways are in ongoing clinical trials, and preliminary data offer hope for greater clinical efficacy in HS in the future.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, debilitating, inflammatory skin disorder of mainly flexural sites bearing apocrine glands, including the axilla, inframammary, and anogenital regions. Typical early lesions are solitary, painful nodules that may persist for weeks to months, with a mean duration of 7 to 15 days (1). These nodules can fail to rupture and resolve spontaneously (i.e., silent nodules) or evolve into abscesses (1). Abscesses can rupture spontaneously or after incision, followed by drainage of purulent material (1). Chronic inflammation can result in the formation of chronic sinuses that tunnel into neighboring skin, resulting in chronic discharge and malodor from anaerobic bacterial colonization (1) (**Figure 1**). Healing with hypertrophic scarring and multiporous or uniporous "tombstone" open pseudocomedones is characteristic (1). Folliculitis, or follicular pustules, can also co-occur but are not a diagnostic feature of HS (1).

The topographical distribution of lesions differs between men and women. Women report more lesions on the anterior part of the body (axillae, breasts, and genitofemoral area), while men report more involvement of the back of the body and atypical sites such as the ears and chest, as well as the presence of a pilonidal sinus (2, 3). Because the diagnosis of HS is made clinically, a standard disease definition is essential for the accurate determination of prevalence and incidence. Three criteria must be met for HS to be diagnosed: (*a*) typical inflammatory skin lesions, as described above; (*b*) occurrence in one or more sites of predilection, predominantly flexural sites, in particular the axillae and groin; and (*c*) chronic or recurrent bouts of inflammation (4).

EPIDEMIOLOGY

Determination of HS prevalence and incidence is challenging because the disease is often under-recognized, and diagnostic delay is common (6). Prevalence figures vary greatly in the literature

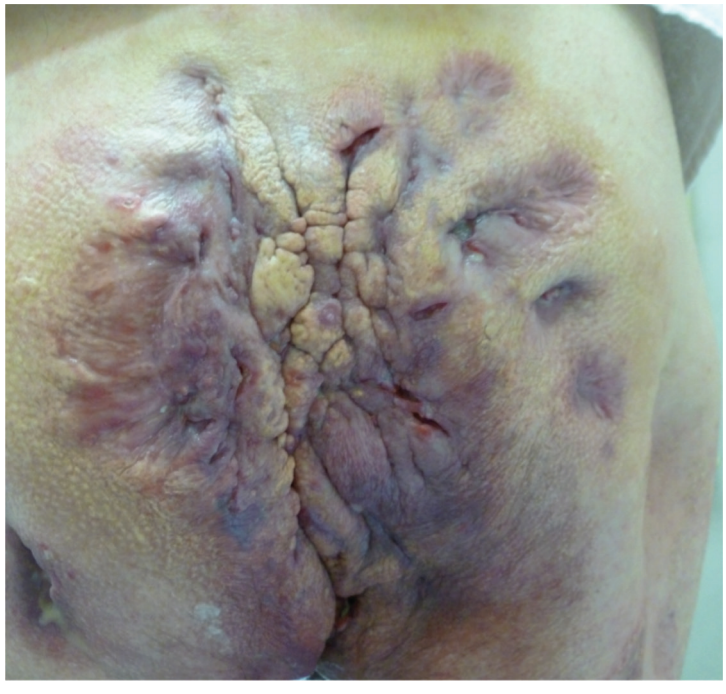

Figure 1

Severe Hurley stage III hidradenitis suppurativa of the buttocks. Figure adapted from Reference 5.

from 0.05% to 4.1%, probably as a result of different data sources and the varying levels of HS recognition between countries (7–9). The incidence of HS appears to be increasing, possibly because of the increasing recognition of the condition (7). The annual incidence of HS is 11.4 per 100,000 people in the United States and 28.3 per 100,000 people in the United Kingdom (10, 11).

Women are more commonly affected than men (12). In Europe and North America, HS has a female-to-male ratio of 3:1 (7, 13, 14). Interestingly, however, in South Korea the ratio is 1:1.6, with a more common presentation in males (13). HS is reportedly associated with lower socioeconomic status, which may relate to the higher prevalence of risk factors for developing HS in this group or be a consequence of the illness itself (15).

ETIOLOGY AND PATHOGENESIS

Our current understanding of the etiology and pathogenesis of HS is incomplete. Numerous hypotheses exist concerning the interplay of lifestyle factors, the skin microbiota, genetics, and a dysregulated immune system (16).

Two lifestyle factors that are widely accepted to play a role in the development of HS are obesity and tobacco smoking. A higher pack-per-year smoking history and a higher body mass index are linked to increased disease severity (10, 17, 18).

Hormones also appear to play a role. HS demonstrates a female predominance and presents mostly after puberty. Patients often report premenstrual flares when progesterone levels are high (19).

A family history of HS is reported in approximately 40% of cases, demonstrating a genetic predisposition (20). Familial HS tends toward more severe disease and lower remission rates, implying the importance of genetic factors (20). Interestingly, patients with no family history of HS tend to be more overweight and smoke more, suggesting that different subpopulations of HS patients exist (21). A recent study (22) calculated the heritability of HS to be 77% (95% confidence interval, 54–90%), suggesting that genetic factors contribute strongly to the development of HS. The heritability of HS is higher than that of psoriasis and rheumatoid arthritis (22) but, interestingly, similar to that of Crohn's disease (CD) (22). Defects in the Notch and γ-secretase pathways have been described (23–25); however, γ-secretase mutations appear to represent only a minority of HS cases, even in those with a family history (26, 27). Mutations in γ-secretase can also be present in unaffected family members, suggesting incomplete penetrance; epigenetics, such as the impact of smoking, may be important for the development of HS in these cases (28). Mutations in proline-serine-threonine phosphatase–interacting protein 1 (*PSTPIP1*) have been identified in syndromic cases of HS (29).

HS was once believed to be a disease of the apocrine gland; however, it is now known that it is mainly a disease of the hair follicle (30). The primary event in HS is follicular occlusion with infundibular hyperkeratosis of the follicle and hyperplasia of the follicular epithelium, which lead to the collection of cellular debris, dilation of the hair follicle, rupture, an inflammatory response, abscess and sinus tract formation, and scarring (31).

HS was largely thought to be an infectious disease until the 1980s, when early studies suggested that immune dysfunction, particularly T lymphocytes, plays a role in its pathogenesis (32, 33). In the primary lesion, the release of follicular contents into the dermis activates several inflammatory pathways, particularly the T helper 17 (Th17)/interleukin (IL)-23, NOD (nucleotide-binding oligomerization domain)-like receptor protein 3, and innate Toll-like receptor pathways, causing skin inflammation and an inflammatory loop (34). The resulting influx of dysregulated immune cells and the production of keratinocyte-mediated products are key to the development and maintenance of inflammation in HS (35, 36).

Studies determining the levels of cytokines in the serum and skin, both affected and nonaffected, have led to a greater understanding of HS pathogenesis. Elevated cytokine levels have been observed in the affected and unaffected skin, serum, and exudate of HS patients (35, 36). Cytokines can contribute to follicular occlusion in the primary lesions by contributing to hyperkeratinization and hyperplasia of the follicular infundibulum (37). Furthermore, circulating cytokines and chemokines are thought to prompt the development of HS in distant predilection sites (34). Cytokines that are elevated in HS include IL-1α and -1β (36, 38); IL-36α, -36β, and -36γ (39); tumor necrosis factor α (TNF-α) (40, 41–43); interferon γ (44, 45); IL-10 (36); IL-12 and -23 (46); and IL-17 (47).

The role of the skin microbiota in the development of HS is an area of expanding research. However, its role in the development of HS is controversial (48). Several studies have reported that the microbiomes of HS lesional and nonlesional skin differ from those of healthy controls and support a role for the microbiome in disease pathogenesis (e.g., 49). Nevertheless, HS does not appear to be a primarily infectious disease (50). The response to immunosuppression also suggests that the role of the microbiota is not the primary cause of HS but rather a contributing factor (51). Furthermore, we do not know whether antibiotics are effective in HS because of their antibacterial or anti-inflammatory properties (52). Antibiotics may attenuate the inflammatory response in HS by removing bacteria from ruptured follicles, which are thought to trigger an immune response (53).

ASSOCIATED CONDITIONS

Autoinflammatory diseases are a heterogeneous group of systemic disorders characterized by an exaggerated innate immune system response with abnormal IL-1 signaling (54). The four recognized autoinflammatory syndromes presenting with HS as part of the spectrum of disease are PASH (pyoderma gangrenosum, acne, and HS), PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, and HS), PsAPASH (psoriatic arthritis, pyoderma gangrenosum, acne, and HS), and PASS (pyoderma gangrenosum, acne, and ankylosing spondylitis, with or without HS). They are associated with mutations related to the inflammasome, which regulates innate immunity. Diagnosis of syndromic HS is often based on clinical features, which may be atypical, severe, and resistant to treatment, and on the presence of systemic inflammation.

HS is strongly associated with acne vulgaris (37), pilonidal sinus (27, 30, 49, 55), and dissecting cellulitis of the scalp (56). The clinical features of HS overlap with those of dissecting cellulitis, HS, and acne conglobata, which are known as the follicular occlusion triad (or tetrad if pilonidal sinus is also present) (56).

HS and inflammatory bowel disease (IBD), in particular CD, share clinical and pathogenic similarities and are known to be associated (57, 58). A CD prevalence of 2% in patients with HS has been reported in the United States, compared with 0.6% in controls, and the prevalence in European patients with HS is higher at 2.5% (59, 60). In Korean patients, no association between HS and CD has been found, but there is an association with ulcerative colitis (13). Data from meta-analyses demonstrate 2.12-fold-increased odds of developing CD and 1.51-fold-increased odds of developing ulcerative colitis; one cohort demonstrated a 5.6-fold-increased risk of IBD in patients with HS (57).

HS has been associated with metabolic syndrome (18), type 2 diabetes mellitus (18, 61), and cardiovascular disease (62). Polycystic ovarian syndrome is also commonly associated with HS; however, studies of this link are lacking (63, 64).

DISEASE SEQUELAE

A rare complication of the chronic inflammation in HS is the development of cutaneous squamous cell carcinoma (SCC). Men have a higher risk of developing SCC in HS, and older patients

and nearly all cases of SCC in the literature involved the perianal or buttock regions (65). Patients often present late because of the difficulty of distinguishing early SCC with HS lesions, and more than half of the cases in the literature presented with metastases (65). It is imperative that patients be monitored for malignant transformation of chronic lesions to ensure early diagnosis and treatment.

Lymphedema, characterized by swelling and induration of the skin, is a recognized complication of HS that can be difficult to treat (66). Lymphedema frequently complicates HS of the genital area and buttocks (66). Once lymphedema is established, it responds poorly to HS medical management (66). Early intervention in HS should be undertaken to prevent lymphedema, and once it is present, early surgical intervention should be considered (66).

HS is a debilitating, painful, and chronic skin condition, and the drainage and odor from suppurating lesions can cause embarrassment and social isolation. It is therefore unsurprising that patients with HS have a high prevalence of depression and anxiety (67). The literature also reports a higher risk of suicide (68).

Additional consequences of the disfigurement and painful inflammation of HS are poor body image and sexual dysfunction. Body image is significantly diminished in patients with HS compared with body mass index–matched controls (69). Sexual dysfunction is markedly raised in HS, with a reported prevalence between 51% and 62% (70). Risk factors for sexual dysfunction in HS included female sex, more severe disease activity with active lesions in the genital area, higher intensity of pain, presence of malodor, and presence of mood disorders (70).

MANAGEMENT

Due to the phenotypic heterogeneity of HS and its multifactorial pathogenesis, it is unsurprising that HS is a complex disease that can prove challenging to manage. Treatment options include lifestyle measures (weight reduction and smoking cessation); topical antiseptics (e.g., chlorhexidine); topical antibiotics (e.g., clindamycin); intralesional steroid injections; and systemic medications including antibiotics, retinoids (acitretin), and hormonal therapies (metformin and antiandrogens) (71, 72). Surgical procedures include incision and drainage, wide local excision, and use of ablative lasers to treat irreversible lesions in combination with medical management (73).

Systemic Antibiotic Therapy

Systemic antibiotics are indicated in patients with mild disease that fails to respond to topical or lifestyle measures, moderate to severe disease, and involvement of multiple body sites (74–75). Monotherapy may be effective in mild to moderate disease; however, in more advanced disease it is used as an adjunct to other therapies. Antibiotics are thought to be effective in HS because of their anti-inflammatory properties, but antibiotics that lack anti-inflammatory action, such as ertapenem and ceftriaxone, are also effective (52, 76).

Tetracycline antibiotics or combination therapy with rifampicin and clindamycin for a 12-week period are the first-line choices as monotherapy for HS. They can be used as an adjunct in more severe disease (72).

Intravenous antibiotics, such as induction therapy with intravenous ceftriaxone (78), have also been used in HS. Intravenous ertapenem daily for 6 weeks is also effective; one study showed dramatic improvement in severe cases (76). As a result, intravenous ertapenem is used as a bridge to biologic or surgical treatment of severe HS (76).

Management of Moderate to Severe Hidradenitis Suppurativa

Targeted biologic therapy is now the mainstay of treatment of moderate to severe HS. The anti-TNF-α antibody adalimumab and the anti-IL-17 secukinumab, which are the only two

biologics approved for HS by the US Food and Drug Administration and the European Medicines Agency, show moderate efficacy of approximately 50% in placebo-controlled studies (40, 77). Drugs targeting the IL-17, IL-36, complement, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways are the focus of current and future research.

The use of adalimumab is based on the results of two phase III, double-blind, placebo-controlled trials (PIONEER I and II) (40). In these studies, 633 participants with HS received either (*a*) a loading subcutaneous adalimumab dose of 160 mg at week 0 and 80 mg at week 2, followed by a 40-mg weekly maintenance dose starting at week 4, or (*b*) a placebo. In PIONEER II, tetracycline antibiotics were continued if required (40). A clinical response of at least a 50% reduction in the number of abscesses or inflammatory nodules with no increase in draining fistulae ($HiSCR_{50}$) was achieved in 50.6% of participants on adalimumab versus 26.8% receiving a placebo ($p < 0.001$). Dermatology Life Quality Index scores also improved in the treatment arm (40). A total of 88 participants entered the open-label extension study of adalimumab 40 mg weekly; 52.3% achieved $HiSCR_{50}$ at week 12, 62.5% at week 36, and 52.3% at week 168 (79). In practice, doses of 80 mg weekly can be introduced in patients with partial response or loss of efficacy to 40 mg weekly of adalimumab (80).

Secukinumab, a human monoclonal immunoglobulin G, subclass 1, κ light chain (IgG1κ) antibody that binds IL-16, has shown similar efficacy in HS. The SUNSHINE (778 participants) and SUNRISE (780 participants) trials compared secukinumab every 2 weeks (Q2W) and every 4 weeks (Q4W) with a placebo (77). Patients in the Q2W arm achieved $HiSCR_{50}$ in both studies, but those in the Q4W arm achieved $HiSCR_{50}$ in the SUNRISE trial only [45% for Q2W ($p = 0.0070$), 42% for Q4W ($p = 0.042$), and 34% for the placebo in the SUNSHINE trial; 42% for Q2W ($p = 0.015$), 46% for Q4W ($p = 0.0022$), and 3% for the placebo in the SUNRISE trial] (77). HS is associated with IBD, as discussed above, and careful clinical examination to detect possible susceptibility to IBD prior to IL-17 therapy is advisable (81). The SUNRISE trial observed three cases of new-onset IBD (77). IL-17 therapy should also be avoided in patients with active IBD.

New and Emerging Treatments

A number of promising new therapies are currently under investigation for the treatment of HS.

Interleukin-17 family cytokines. Bimekizumab is a monoclonal IgG1 antibody that inhibits IL-17A and IL-17F. A phase II, double-blind, placebo-controlled trial compared bimekizumab 640 mg at week 0 followed by 320 mg Q2W; adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg weekly starting at week 4; and a placebo (82). Of the patients receiving bimekizumab, 57.3% achieved $HiSCR_{50}$ at week 12 versus 26.1% in the placebo group; 46% of the bimekizumab-treated patients achieved $HiSCR_{75}$ and 32% achieved $HiSCR_{90}$; 10% of placebo-treated patients achieved $HiSCR_{75}$ and none achieved $HiSCR_{90}$; and 35% of adalimumab-treated patients achieved $HiSCR_{75}$ and 15% achieved $HiSCR_{90}$ (82). Preliminary results from a phase III trial demonstrate a greater $HiSCR_{50}$ response to bimekizumab Q2W versus a placebo in BE HEARD I (47.8% versus 28.7%) and BE HEARD II (52% versus 32.2%) (83) (**Table 1**). Izokibep, a synthetic ligand trap that is a potent and selective inhibitor of IL-17A (NCT05355805), and sonelokimab, a nanobody that selectively binds to IL-17A and IL-17F (NCT05322473), are also being studied in HS.

Interleukin-1 family cytokines. The IL-1 pathway is hyperactive in HS, leading to skin infiltration and destruction (84). Studies have evaluated the possibility of targeting this pathway in HS. A phase II trial of lutikizumab, an anti-IL-1α/β dual-variable-domain immunoglobulin, is ongoing (NCT05139602).

Table 1 Results from new and emerging therapies in HS

Agent	Target	RCT phase	Intervention	*N*	Primary endpoint	Results	Reference
Bimekizumab	IL-17A/ IL-17F	III	Bimekizumab 320 mg Q2W or 320 mg Q4W	505	$HiSCR_{50}$	Q2W: 47.8% Q4W: 45.3% Placebo: 28.7%	82
			Bimekizumab 320 mg Q2W or 320 mg Q4W	509	$HiSCR_{50}$	Q2W: 52% Q4W: 53.8% Placebo: 32.2%	82
Povorcitinib	JAK1	II	Povorcitinib 15, 45, or 75 mg OD	209	Change from baseline AN count at 16 weeks	15 mg: −5.2 ($p = 0.0277$) 45 mg: −6.9 ($p = 0.0006$) 75 mg: −6.3 ($p = 0.0021$) Placebo: −2.5	85
Brepocitinib	TYK2/ JAK1	II	Brepocitinib 45 mg OD	52	$HiSCR_{50}$	Brepocitinib: 51.9% Placebo: 33.3%	87
Upadacitinib	JAK1	II	Upadacitinib 30 mg OD	68	$HiSCR_{50}$	Upadacitinib: 38.3% ($p = 0.018$) Placebo: 25%	86
Spesolimab	IL-36R	II	Spesolimab 1,200 mg Q2W	52	Change from baseline AN count at 12 weeks	Spesolimab: −38.8% Placebo: −34.7%	84

Abbreviations: AN, abscess and nodule; $HiSCR_{50}$, HS clinical response of at least a 50% reduction in the number of abscesses or inflammatory nodules with no increase in draining fistulae; HS, hidradenitis suppurativa; IL, interleukin; JAK, Janus kinase; OD, once daily; Q2W, every 2 weeks; Q4W, every 4 weeks; RCT, randomized controlled trial; TYK, tyrosine kinase.

IL-36 is involved in neutrophil recruitment and activation and is induced by IL-1β (85). Elevated levels of IL-36 have been found in HS lesions (85). Spesolimab, a monoclonal antibody that binds to IL-36, was developed for the treatment of pustular psoriasis (86). A phase II study demonstrated a percentage change in abscess and nodule count of −38.8% in patients randomized to receive spesolimab versus −34.7% in the placebo arm (87) (**Table 1**).

Janus kinase inhibitors. JAK inhibitors block IL-6 signaling through the JAK/STAT pathway (88). Povorcitinib (INCB054707) is a selective JAK1 inhibitor. A phase II trial showed greater decreases from baseline in abscess and nodule counts versus a placebo (89) (**Table 1**). Two phase III trials to further assess the efficacy of povorcitinib are ongoing (NCT06212999, NCT05620836).

Another JAK1 inhibitor, upadacitinib, has been studied in HS in a phase II trial (90) where 38.8% of patients achieved $HiSCR_{50}$ at week 12 versus 25% of patients receiving a placebo. This result supports further investigation of the use of upadacitinib in HS (90) (**Table 1**).

CONCLUSIONS AND RECOMMENDATIONS

HS is a chronic, debilitating disease, and its pathogenesis is still not completely understood. HS is likely the result of several different factors, including immune dysregulation and an altered microbiome, so multimodal treatments are likely to be the way forward in the future. Patients often present late, and a delay to diagnosis is common (6). Therefore, efforts should be made to diagnose HS early to prevent progression of disease. HS can also prove challenging to treat, especially in comparison to psoriasis. A lack of standardized outcome measures in older HS trials hindered comparisons of clinical data, making the development of evidence-based guidelines challenging (92). Moreover, only two approved biologics are currently on the market (40, 77). However, the

number of clinical trials, including those targeting the IL-17, IL-36, and JAK/STAT pathways, has rapidly increased in recent years. The higher thresholds of the primary endpoints in unpublished clinical trials that are currently recruiting show promise for more effective HS therapies in the future.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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