

Hidradenitis suppurativa; classification, remedies, etiology, and comorbidities; a narrative review

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that is more common in females, especially during puberty and menopause. These inflammatory lesions include painful deep-seated nodules and abscesses, draining sinus tracts, and fibrotic scars. This article is a narrative review to explain whole disease aspects, including complication, causes, epidemiology, history, classification, prognosis, comorbidities, the effect of sex hormone, and potent treatments. Most patients with HS, who are not aware of their primary disease, visit primary care physicians to superinfection lesions instead of specialists. If these physicians suspect HS, their illness will not get misdiagnosed. This brief and comprehensive information in this article may help doctors to decide better about the same situation.

Keywords: Acne inversa, causes, comorbidities, hidradenitis suppurativa, relation to sex hormone, treatment

Introduction

First, the term hidradenitis suppurativa (HS) has three parts that describe this disease perfectly: Hidros meaning “sweat,” Aden meaning “gland,” and Suppurative meaning “with pus.” However, it is a disorder of follicular unit and not sweat glands. HS is also called acne inversus. For more details, HS is a chronic, debilitating disorder affecting the follicular part of the

folliculopilosebaceous unit and manifested as painful suppurative lesions such as deep-seated nodules and abscess, draining sinus tracts, and fibrotic scars in areas having more receptors for androgen and sex hormones than other parts of the skin or where two layers of skin rub against each other such as the axillary or inframammary location. Pathologists have implicated that HS is caused by chronic inflammation with architectural tissue changes and follicular hyperkeratosis, dilatation, and follicular rupture.^[1]

The prevalence of HS is higher in females than males (about three times more common). Even HS can occur before puberty,^[2] especially among obese children; it is more common between puberty and menopause. Besides, most of the recurrences occur a few days before menstruation and last until its end. Some comorbidities associate with androgen excess such as metabolic syndrome, obesity, polycystic ovarian syndrome, and some other complications such as excessive sweating, increased pain sensitivity, and depression that can vindicate the theory of setting

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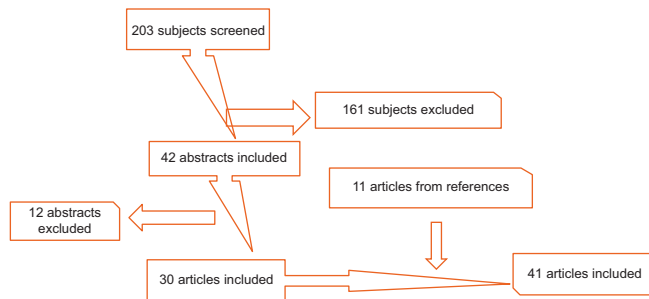
sex hormone as one of the reasons.^[1] HS causes psychological problems that add to physical complications and decrease work productivity. The curability of HS with early diagnosis and the start of proper medications is a fact that has stimulated many researchers to discover more features of this disease.

This article is a narrative review to explain whole disease aspects, including complications, causes, epidemiology, history, classification, prognosis, comorbidities, and association of sex hormones, to offer effective treatments.

Methods

A narrative review using PubMed and StatPearls database was conducted with the search term “hidradenitis suppurativa,” and from 203 original case reports and reviews in English and Persian languages published between 2004 and 2021. In total, 44 articles were selected.

According to the quality of research available and quantity of sample volume, the articles were selected while preferring recent analyses and more related to hormonal disorders. Some case reports were used to complete the content when the references became limited and sparse. The articles were included by searching Google and PubMed and using EndNote X9 and Google Scholar.



Complications

Physical condition

1. Lesions included abscesses, tracts, and tunnels (source of inflammation),^[3] rope-like scars, and pitted skin (blackheads). HS usually appears as a single, painful lump under the skin that lasts for weeks or months. It extends into the sweat glands in areas with hair follicles such as the armpits, groin, and anal area. They are also observed where the skin rubs together, such as the inner thighs, breasts, and buttocks.
2. Chronic pain, limb contractures, impaired mobility, and movement restriction.
3. Peripheral lymphedema, swelling in the legs, arms, and genitals (caused by lymphatic obstruction)
4. Anemia, hyperproteinemia, amyloidosis, axial and peripheral arthropathy (caused by chronic inflammation)
5. Systemic illness (caused by superinfection)
6. Squamous cell carcinoma, buccal and hepatocellular cancer (increased risk of malignancy)
7. Superinfection in inflamed areas

8. Chronic inflammation of Uvea or uveitis: rare but severe cases^[4]
9. Nonalcoholic fatty liver disease (NAFLD), maybe because of metabolic syndrome^[5]
10. Interstitial pneumonia: a dense pulmonary infiltration consisting of neutrophils, lymphocytes, and scattered plasma cells and fibrosis. HS is known as a neutrophil-mediated auto-inflammatory disease.^[1]
11. Acne keloidalis nuchae^[5-7]

A psychological condition related to chronic pain, odor, drainage, deformity of skin in particular areas:

1. Depression
2. Social isolation
3. Sexual dysfunction
4. Decreased work productivity
5. Suicide.

Etiology

Although the pathogenesis of HS is still unclear, follicular occlusion caused by infundibular keratosis and hyperplasia of epithelium is thought to be the first event in the HS mechanism. According to observation, some factors make or exacerbate HS:

1. Genetics; data indicate that one-third of patients with HS have the same symptoms in their families.^[8] Also, some genes, such as γ secretase family (NCS1N, PSEN1, PSENEN, and POGUT1), are supposed to be responsible for this disease,^[9,10] and autosomal dominant mutations affect the downstream Notch signaling in the skin. Mutations associated with monogenic autoinflammatory disorders (e.g, MEFV, NLRP3, NLRP12, NOD2, LPIN2, and PSTPIP1) are manifested in the syndromic type of HS.^[11,12]
2. Immune system; recent studies suggest autoimmunity causes for HS, including innate immune and adaptive immune systems (however, HS is largely classified as a neutrophilic disorder). They found neutrophil extracellular traps (NET), INF1 signature, an association between sinus tracts, and scarring with MMP-2 and TGF- β and ICAM-1 signaling and proved the role of the innate immune system. In contrast, increasing IL-1, IL-10, IL-12, IL-17, IL-23,^[13] TNF, caspase-1, S100A8, and S100A9 levels in the inflamed tissue also increase the activity of dendritic cells and T cells (especially Th17),^[14] demonstrating the role of the adaptive immune system. According to this evidence, autoinflammation is believed to play a fundamental role in HS, especially in patients with the syndromic phenotype.^[15-17]
3. Bacteria; bacterial infections were believed to be the reason for HS disease in the past decades. However, this cause is doubted by recent studies because of sterile cultures of lesions^[18,19] and the inefficacy of antibiotic treatment to cure many patients.^[20] It also suggests that infection might be the second event after starting HS. In contrast, theories of bacterial infections have been accepted again. In contrast, different cutaneous microbiomes (dysbiosis) in patients with HS have been observed.^[21] It is suggested that overacting immune systems (such as suppression of Tregs) can cause HS^[22] to explain the effects of antibiotics in some other patients. It is recommended that antibiotics such as rifampin may prevent secondary infections that exacerbate HS.

4. Androgens and estrogens; many women have reported exacerbation of HS during premenstrual periods, and remission has been observed during pregnancy. Decreased levels of progesterone and estrogen and increased levels of androgens have been observed in HS flares before menopause. Although some studies reported the same results about menarche in both patients with HS and controls, early onset of menarche seems to be related to familial forms of HS and more widespread lesions.^[18]

Premenstrual hormone levels are characterized by a sudden drop in both estradiol and progesterone levels, suggesting that hormonal changes during the menstrual cycle can affect the onset and symptoms of HS.

Nowadays, the effects of hormone therapy such as testosterone and finasteride (interact with androgens) have become one of the most controversial questions.

5. Lifestyle; wearing tight clothes is believed to increase friction. Some women have found that using tampons compared to sanitary pads reduces friction with the skin, and using washcloths, loofahs, or other items can irritate the skin on affected areas. Squeezing the pimples, sores, and shaving affected parts could result in recurrence. Poor hygiene is not a cause for HS, but using soap cleansers and shaving a lot could stimulate the immune system and be a reason for HS.^[19]
6. Mechanical stress; many skin disorders are due to mechanical stress. Friction can cause tissue ischemia in skin breakdown and HS, according to the resistance to motion in a direction relative to the common boundary of two surfaces. Conflict may occur in areas with continuous skin contact with external materials (such as a dress) or skin of other areas (skin-to-skin). Body areas with the most significant risk are the axillae, groin, buttocks, neck, and waistline.^[20]
7. Mental stress; like other inflammatory diseases, HS symptoms might appear or worsen with mental stress and anxiety.^[21]
8. Smoking; More than 70% of patients with HS are smokers. Smoking cigarettes is linked to an increased prevalence of HS and more severe HS symptoms.^[8] Several studies suggest that smoking may directly affect the HS process,^[22] including exacerbating follicular plugging, changing neutrophilic granulocytes and sweat gland activity, and weakening the host innate immunity or oxidant-Toll-like receptor interactions that supply pro-inflammatory signals.^[23]
9. Diet; HS symptoms may worsen by eating meals with a high glycemic index such as dairy and red meat. Foods containing dairy and sugar can raise your insulin levels^[24] and cause your body to overproduce certain hormones called androgens, potentially making your HS worse.^[25] They also indicate that brewer's yeast, a common ingredient in bread, beer, and pizza dough, can cause severe reactions in some people with HS.

Some studies indicate that Crohn's disease can cause HS symptoms, so inflammatory bowel disease and patients should avoid stimulating foods such as pepper and spicy ones, pastry, and chocolate. Also, following a healthy diet can help losing weight too. Ramadan fasting (intermittent circadian

fasting practised every year by the Muslim population) is safe and effective in HS patients.^[26,27]

10. Obesity; studies have shown that people who are obese have a higher chance of developing HS and tend to experience more severe symptoms. Several studies indicate the relation between BMI and HS severity.^[8,22,28] Because HS flares up from one area of the body where the skin rubs against the other part of the skin, the friction and the added potential for bacterial growth created by excess skin folds can increase the likelihood of HS flare-ups.^[29,30]
11. Weather; some people experience breakouts when exposed to hot and humid climates. Dabbing away sweat with a soft towel helps to keep your skin dry. Certain deodorants and antiperspirants have been known to irritate underarm areas, thus making one prone to HS breakout.^[31]

Epidemiology

HS has been known as an independent disease for decades, and the epidemiologic data were sparse and limited because of misdiagnosis.

The prevalence rates for HS are estimated to be 1% in the general population although the true percentage might be higher. Recent researches show that the incidence of HS has become more than doubled from 1986 (4.0 patients per 100,000) and 2008 (10.0 patients per 100,000) to 2021 (the global prevalence is estimated to be 0.00033–4.1%),^[1] which is the result of improvement in diagnosis and informing people about this skin disease.^[32,33] Studies showed that HS is three times more common in women than men; however, in some countries such as Tunisia, HS is more common in men. They also found out that men have more severe complications than women and the lesions appear in atypical areas (gluteal). These differences may be because of follicular trauma, shaving, skin microbiome, adipose tissue, lifestyle, the time of seeking a cure; the primary reason is the level of hormones. Both men and women have responded well to antiandrogen medications despite all differences. HS can begin before and after puberty; however, most studies indicate that the average onset is after puberty (in the early 20s), and the peak of inflammations is in the third or fourth decade of life. HS usually occurs after menopause spontaneously.^[34] Most patients suffer from mild to moderate symptoms, and in contrast, a severe disease has been reported in 4 to 22% of patients.^[22]

Classification and Treatments

According to the area of the lesion, HS has three subtypes:

1. Axillary–mammary (48%): most common subtype, the typical one.
2. Follicular (26%): inguinal and inframammary folds, atypical and follicular lesions (e.g., pilonidal sinus, comedones, and severe acne) affect male patients and associate with smoking, positive family history, and early onset of the disease, which has more severe complications.

3. Gluteal (26%): patients with lower BMIs and less severe symptoms.
4. Using adalimumab in the early phases of HS is more effective, and the therapeutic delay correlated to lack of clinical response to adalimumab, especially at week 16 of the treatment.^[35]

The most useful classification is Hurley stages, which determine the appropriate treatment:

Hurley stage	Medication/ regimen	Comments	Extent of HS
I	1. Topical clindamycin 1% BID during flares, daily for maintenance 2. Intralesional corticosteroids (triamcinolone 10 mg/mL) 3. Topical 15% resorcinol BID if the patient complains of headache, vomiting, and has flares, risk of infection ^[36] 4. Punch debridement (new inflamed nodules without sinus tracts) ^[37]	1. Well-tolerated 2. Hypopigmentation and atrophy of the skin can occur. Sterile abscess formation is less frequent 3. Irritant contact dermatitis 4. Recurrence is common in incised nodules	Isolated lesions
II	1. Oral antibiotics: Doxycycline 100 mg daily or BID. Minocycline 100 mg daily or BID. Tetracycline 500 mg BID ^[38] 2. Clindamycin 300 mg BID + rifampin 600 mg daily ^[39,40] 3. Dapsone 50-200 mg daily ^[41] 4. Acitretin 0.56±0.08 mg/kg daily ^[42] 5. Hormonal therapy (e.g., oral contraceptive pills) ^[43] 6. Spironolactone 100 mg Daily ^[34]	1. Patients should wear sunscreen and sun-protective clothing because of photosensitization; nausea, pseudo-tumour cerebral, and hyperpigmentation of tissue 2. Pseudomembranous colitis (Clindamycin). Increasing cytochrome p450 activity, red urine, and nausea (Rifampin) 3. Patients with Favism can show hemolytic anemia 4. Redness, itching, dry skin, triglycerides elevating, contraindicated in pregnancy 6. Contraindicated in pregnancy and gynecomastia in men	Widely separated lesions

Contd...

III	1. Adalimumab 40 mg weekly ^[44] 2. Infliximab 5 mg/kg at weeks 0, 2, and 6 ^[45,46] 3. Prednisone 40-60 mg for 3-4 days with a 7-10 day taper 4. Ustekinumab (45-90 mg at weeks 0, 4, 16, and 28) 5. Anakinra 100 mg daily	1. Injection site reaction, headache, +ANA, elevated CPK, psoriasis flare-up. Because of the risk of the infection, patients must test for latent tuberculosis and hepatitis before use 2. The same as adalimumab, it has the risk of infection, headache, nausea, increased alanine aminotransferase 3. Only be used for severe inflammatory cases due to unpleasant side effects 4. Risk of infection 5. Risk of infection; headache, vomiting, and injection site reaction	Diffuse/ near diffuse involvement across a regional area with interconnected lesions
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Other tools that may be used to determine the severity of your HS include the following:

1. Sartorius HS Score that counts and assigns scores to lesions based on tunnels, scarring, and their distance from each other
2. Visual analog scale (VAS) for pain
3. Dermatology Life Quality Index (DLQI), a 10-question questionnaire
4. Hidradenitis Suppurativa Impact Assessment
5. Hidradenitis Suppurativa Symptom Assessment
6. Acne Inversa Severity Index (AISI)

Comorbidities

1. Metabolic and cardiac comorbidities; there is an association between HS and obesity, which causes the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha and IL-6 by adipose tissues, leading to an increase in the prevalence of metabolic syndrome and hypertriglyceridemia, low high-density lipoprotein in patients with HS.

Some other studies indicated a significantly increased risk of cardiovascular disorders, such as ischemic stroke and myocardial infarction. Despite the higher mean resting heart rate in patients with severe HS compared with controls, the mean QRS duration lasts shorter in the group with mild HS.

2. Endocrine comorbidities or some hormone dysfunction have been observed in HS, such as PCOS, associated with obesity and metabolic syndrome, similar to HS.

The prevalence of PCOS among patients with HS is 9.0%. In contrast, it is 2.9% in patients without HS (with odds 2.14 times greater than those without HS). A Danish study showed the relationship between HS and thyroid

dysfunction, which indicated a significantly lower level of TSH and a higher total T_3 level in patients with HS compared with the general population. HS is more accompanied by hyperthyroidism than hypothyroidism, which suggests the association between HS and a hypermetabolic state.

3. Gastrointestinal comorbidities; smoking and genetics are considered risk factors for Crohn's disease and HS. Also, fistula formation is a common HS feature that indicates an association between HS and Crohn's disease.^[47] Another study showed that the prevalence of Crohn's disease was 0.8% among HS patients compared to 0.3% in the general population. In contrast, ulcerative colitis was 1.3% for HS patients versus 0.3% for the general population.^[32] Immune dysregulation is believed to be the reason for the relationship of the increased risk of new-onset of both Crohn's disease and ulcerative colitis among patients with HS. The response to TNF alpha inhibitors in both IBD and HS patients indicates the role of cytokines such as IL-1 beta and IL-17 in both diseases.^[48]
4. Rheumatologic comorbidities; 28.2% of HS patients in a cohort study had spondyloarthritis, compared to 2.6% in the control group.^[49] Axial spondyloarthritis was the most common type.^[50,51] In contrast, the prevalence of HS in axial spondyloarthritis was 9.1% in another cohort study.^[49] Other rheumatoid diseases such as systemic lupus erythematosus have been observed at a higher frequency in patients with HS.
5. Psychiatric comorbidities; according to psychiatric complications, many studies were conducted based on psychiatric comorbidities, which noted a decreased quality of life in patients with HS according to factors such as impairment of sex life, absenteeism from work, unemployment, and feelings of isolation.^[52] Male patients complained of sexual dysfunction, and female patients with HS reported greater levels of sexual distress compared with control groups.^[53] Although patients with HS are using the antidepressant drug more than the general population, HS was not significantly associated with depression or hospitalization due to depression. Because of physical and psychiatric disease burdens, patients with HS were at the most significant risk for alcohol, opioid drugs, and cannabis misuse. Also, studies showed a greater risk of suicide even after adjusting for confounding variables.^[54]
6. Malignancies; the most common malignancy among patients with HS was lymphoma. Studies demonstrated that approximately 2% of HS patients had lymphoma versus 0.5% in the control population (also with 3.6 greater odds of lymphoma in HS patients).^[51] Mostly, non-Hodgkin lymphoma, Hodgkin lymphoma, and cutaneous T-cell lymphoma were reported.^[55] Generating cell populations caused by chronic inflammation is thought to be the reason for this association.
7. Also, more complex autoinflammatory syndromes, such as pyoderma gangrenosum (PASH), acne, and HS or other suppress immune diseases such as familial Mediterranean

fever, according to the pathogenesis of HS, are expected to occur at the same time with these disorders. We can use Autoinflammatory Disease Damage Index (ADDI) as a promising tool to evaluate the long-term systemic outcome in HS.^[56]

Differential Diagnosis

The diagnosis of HS relies on the clinical features, including three criteria:

1. Typical morphology (nodules, abscess, sinus tracts, and scars)
2. Distribution of lesions (intertriginous areas, axillae, inframammary folds, groins, buttocks, perianal and perineal areas)
3. Relapsing and chronic course

Based on these criteria, physicians can distinguish HS from other diagnoses, including:

1. Follicular pyoderma
2. Granuloma inguinale
3. Noduloulcerative syphilis
4. Tuberculous abscess
5. Actinomycosis
6. Lymphogranuloma venereum
7. Acne vulgaris
8. Epidermoid, dermoid, pilonidal, and Bartholin's cysts
9. Crohn's disease^[34,57]
10. Blastomycosis
11. Erysipelas
12. Dermatologic manifestations of nocardiosis
13. Hailey–Hailey disease^[58]

Conclusion

Although HS causes many disease burdens and many studies have been performed, it is not curable entirely. Many comorbidities and triggers have been found, including smoking cigarettes and obesity, which can help to prevent flare-ups and even remission.

The most effective action to control HS is an early diagnosis that leads to start medications and eliminate risk factors. The diagnosis is based on clinical features, and the Hurley stage should choose the treatment. Physicians should acquaint patients with comorbidities, triggers, complications, relapses, and recommendations about lifestyle to reduce anxiety and psychiatric effects.

Key points

1. Hidradenitis suppurativa is a chronic inflammatory skin disease that can be cured with early diagnosis.
2. There is no specific reason for HS; however, it has many comorbidities leading to its pathology.
3. HS is more common among women after puberty to menopause, which indicates the possible relationship between sex hormones and HS. So, hormone therapy can be used as a cure for HS.

Ethical and institutional permission

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Conflicts of interest

There are no conflicts of interest.

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An additional educational challenge to the reader

Choose the best answer:

1. Which one is not a complication of hidradenitis suppurativa?
A) Lesions B) Pain C) Sexual dysfunction D) Pruritus
2. At what age is hidradenitis suppurativa more common?
A) Before puberty B) Between puberty and menopause
C) After menopause D) No difference
3. What is the cause of hidradenitis suppurativa?
A) Bacterial infection B) Dysregulation of sex hormones
C) Immune dysregulation D) All of them
4. A 32-year-old woman suffers from hidradenitis suppurativa for 3 years and has abscess formation without tracts or scars. According to the Hurley staging, what stage is it, and what will you prescribe?
A) Stage 1, topical clindamycin 1% BID during flares B) Stage 1, spironolactone 100 mg daily
C) Stage 3, Prednisone 40–60 mg for 3–4 days with a 7–10 day taper D) Stage 2, hormonal therapy
5. What is the differential diagnosis of hidradenitis suppurativa?
A) Tuberculous abscess B) Hailey–Hailey disease
C) Follicular pyoderma D) All of them

Choose true or false:

6. Hidradenitis suppurativa is more common among women than men. True/False
7. It is believed that smoking is related to the onset and severity of HS True/False
8. Adalimumab can be used to treat the first stage of HS (according to the Hurley staging). True/False
9. Polycystic ovarian syndrome (PCOS) is one of the comorbidities of HS. True/False
10. Losing weight does not seem to be helpful in patients with HS True/False

Answers: 1: D, 2: B, 3: D, 4: A, 5: D, 6: T, 7: T, 8: F, 9: T, 10: F