Hidradenitis Suppurativa: Managing a Complex Disease with Multiple Comorbidities

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Hidradenitis suppurativa (HS), a chronic skin disorder of the intertriginous areas that frequently presents with draining abscesses, deep painful nodules, possible sinus tracts, and the development of widespread scarring, can significantly impact a patient’s quality of life (QoL), therefore early diagnosis and initiation of treatment is vital. This article reviews the existing evidence-based treatment guidelines for HS as described in the literature, stages of HS as categorized by the Hurley system, available treatment options, and short- and long-term disease management strategies, all key to improved patient satisfaction. Common physical and psychological comorbidities of HS, such as hypertension, metabolic syndrome, polycystic ovarian syndrome, depression, and anxiety are also discussed with emphasis on the dermatology physician assistant’s role in comorbidities screening and managing referrals when necessary.

This program has been CME reviewed and is approved for a maximum of 1 hours of AAPA Category I CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of June 1, 2022. Participants may submit the self-assessment exam at any time during that period.

This program was planned in accordance with AAPA’s CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs. SDPA members may access the post-test at https://www.dermpa.org/JDPA_Exams

Learning objectives

1. Discuss the current pathogenesis of hidradenitis suppurativa (HS)
2. Summarize how better understanding of the pathogenesis of HS has led to further, more focused research
3. Describe the Hurley stages and appropriate corresponding treatment modalities
4. Recognize the potential comorbidities associated with HS

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic skin disorder of the intertriginous areas that frequently presents with draining abscesses, deep painful nodules, possible sinus tracts, and the development of widespread scarring. The disease has a persistent course, developing by or within the third decade of life; prevalence is highest in women and African Americans. HS is categorized in stages of severity with ranges of mild to severe. Mild disease refers to a solitary cyst/abscess, and severe disease is the widespread involvement of entire regions with recurrent cyst/abscesses, scarring, and sinus tract formation. Most patients with HS are reported to present with mild to moderate disease.1

To make a significant impact on the quality of life, early diagnosis and initiation of treatment in patients with HS is vital.1 Despite increased awareness of HS, delays in diagnosis and treatment are still being reported.1 Historically, HS has been very challenging to treat; however, research interest about the disease continues to further our understanding of the pathophysiology, treatment, and management recommendations. Greater patient satisfaction is obtainable due to the variety of treatment options now available to the provider based on the prevention of flares and long-term disease management.1,2

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The complete pathophysiology of HS has not been determined. The emergence of information continues to provide new treatment pathways in which to manage patients at any of the three classifications on the Hurley stages of HS grading system (Table 1). The addition of effective biologic medications is changing the treatment landscape for HS, and other biologic treatments in development are showing promising results. In addition, known comorbidities of HS, such as hypertension, metabolic syndrome, polycystic ovarian syndrome, depression, and anxiety, can significantly impact a patient’s quality of life; therefore, the dermatology care provider should also be screening for these and managing referrals when necessary.

### THE PROPOSED PATHOGENESIS

Our understanding of the pathophysiology behind HS continues to evolve. The HS lesion formation involves the pilosebaceous apocrine unit. What is thought to provoke lesion formation has changed over time. It was originally hypothesized that the apocrine gland became inflamed and was the initiating factor in the disease process. However, recent research indicates that hyperkeratosis of the follicle causes plugging and inflammation, and finally, rupture of the follicle is the initial event.\(^1\) Follicle rupture and the ensuing inflammation lead to abscess formation, and sinus tracts can form. After this process, the apocrine gland becomes involved but without changes in size or numbers, and the sebaceous glands, also part of the pilosebaceous-apocrine unit, tend to have a reduction in the number of glands.\(^3\)

Recent research is also investigating the microbiome of HS patients. A basic definition of the microbiome is the collective group of bacteria, fungi, protozoa, bacteriophages, and viruses living on the human skin.\(^9\) When observing skin affected with HS compared to perilesional skin with HS and also skin without HS, the microbiomes are significantly different among the three groups.\(^3,5\) One report states that the commensal bacteria, *Cutibacterium acnes* (formerly *Propionibacterium*), is found in reduced levels in patients with HS, which may be significant because it invites more pathogenic bacteria to colonize the site because of reduction in commensal bacteria.\(^3\) The other notable finding regarding the microbiome is the formation of polysaccharide structures by the bacteria present in chronic HS lesions.\(^3,5\) These structures deposit within the HS lesions, making a protective layer (biofilm) of protection that increases resistance to treatment.\(^5\) Both of these findings have implications that directly impact the development of new treatments. Tobacco can also be associated with HS because of nicotine. Several types of cells reportedly involved in HS pathogenesis have nicotinic acetylcholine receptors, and the induction of infundibular epithelial hyperkeratosis can be shown to be caused by nicotine.\(^3\) Tumor necrosis factor-alpha (TNF-α) responds to increased eccrine gland secretion from nicotine stimulation, and this affects the cutaneous biome.\(^3\)

The genetics of HS is also under investigation. HS occurs in an autosomal dominant pattern, and up to 40 percent of patients afflicted with the disease report having one or more family members with it as well.\(^3\) One gene that has been closely examined in HS is a chromosomal band at the promoter region of the TNF gene.\(^3\) The importance of the role of TNF-α has been paramount in the development of biologic medications in HS. This allowed for the development of a new class of injectable medications, TNF-α inhibitor medications, in the evolving biologic category, to be developed. High levels of TNF-α also appear to correlate with the severity of HS disease.\(^5\) Due to the activation of macrophages, TNF-α, and other cytokines, interleukin (IL)-12 and IL-23, are expressed in HS. Hormone involvement has also been investigated. Studies suggest that there is a hormonal influence with many patients reporting exacerbations of HS flares with menstrual cycles and pregnancy.\(^6\)

### STAGING AND RELATED TREATMENT RECOMMENDATIONS

The Hurley classification is the most common clinical staging scale used for HS in a clinic setting. The scale consists of three stages and a corresponding clinical presentation description. Stage I is the development of nodules or abscesses, which can be single lesions or multiple lesions, without sinus tracts and without scarring. Stage II is one or more separated lesions by region, recurring nodules, abscesses with sinus tracts, and scarring, usually not more than one sinus tract per anatomical site. Stage III represents multiple interconnected tracts and abscesses with extensive scarring throughout an entire area. Definitive diagnosis requires three components: 1) the findings as described in the definition, 2) the predisposition of those findings to be in the intertriginous anatomical sites, and 3) the recurring of the lesions.\(^6\)

Patients with HS require management of their disease, which usually involves more than one prescription or treatment modality. The dermatology provider can use the Hurley stage to guide a customized patient care plan. The treatment goal is to manage the chronicity of the disease. Acute flares, which can happen every few days for some patients, are best managed separately from chronic disease.

**Hurley Stage I.** Stage I HS is often treated with topical therapies. Acute early lesions that are nodules or abscesses can be treated with intralesional corticosteroid injection, punch debridement, and short courses of oral corticos-
rifampin and clindamycin. Efficacy from application of cream has shown oral nisone to be ineffective in Stage II and III. The 1064nm Neodymium-doped yttrium aluminum garnet (ND-YAG) lasers have been shown to have the best efficacy, with four treatments at four-week intervals. This laser is non-ablative, which means it does not damage the outer layer of the skin. Settings used for Fitzpatrick skin types I to III were typically 35 to 50 J/cm2, a spot size of 10 mm, and 10 ms pulse duration. Fitzpatrick skin types IV to VI were used 25 to 240 J/cm2 and 20ms pulse duration. Alternative lasers, such as intense pulsed light (IPL), alexandrite, and diode, have had disappointing results.

Photodynamic therapy (PDT) using either topical or intraleisonal 5–aminolevulinic acid (ALA) can induce bacterial cell death because of the photosensitizing topical chemical applied. The PDT treatment has not been shown to be effective. The penetration of the ALA into the HS lesions is the central issue that has led to the more specific intraleisonal application of the ALA technique to obtain better results. A study showed some increased efficacy using the intraleisonal technique, but the sample size was small. CO2 lasers are typically reserved for excising lesions, and fractionated CO2 lasers can reduce scarring.  

**Hurley Stage II**. Stage II patients with HS may benefit from systemic treatment using oral antibiotic therapy. If a patient has an acute flare, deroof new lesions, oral antibiotics may be initiated, and a short course of oral prednisone can be used in select patients. A tetracycline-class oral antibiotic is suggested to be used first line and has been shown to be effective due to its anti-inflammatory benefits. Most common side effects include nausea, vomiting, dizziness, headache, loss of appetite, and photosensitivity. Contraindications include known drug allergy to tetracycline, liver problems, decreased kidney function, pregnancy, pseudotumor cerebri, or breastfeeding. A 10 to 12-week course is appropriate, and then a break to assess efficacy is recommended. Antibiotics are often prescribed for anti-inflammatory instead of antimicrobial effects, and resistance can be seen. If a tetracycline antimicrobial proves to be ineffective or becomes ineffective over time, there is supporting evidence that the combination of oral clindamycin and rifampin can be beneficial. Clindamycin 300 mg twice daily and rifampin 300 mg twice daily are given concurrently for 10 to 12 weeks. Monotherapy with rifampin should be avoided because of the development of bacterial resistance, and careful attention to the potential for significant drug interaction with rifampin is important. Contraindications to clindamycin include known drug allergy. Side effects include nausea, vomiting, metallic taste, joint pain, pain with swallowing, and heartburn. Contraindications to rifampin include known drug allergy. Side effects include itching, flushing, headache, drowsiness, and dizziness.

Additional treatment options in Stage II may be considered. Isotretinoin (first-generation retinoid) or acitretin (second-generation retinoid) may be considered if the patient also has severe acne and the HS has an acneiform component, which are raised acne-like bumps. Several studies have shown efficacy with both medications. However, many clinicians prefer acitretin due to the differences in its metabolite, but there is no comparative evidence to support its superiority to isotretinoin. A female patient that shows signs of polycystic ovarian syndrome (PCOS) may benefit from the addition of spironolactone. Dosing for spironolactone is typically 100 mg to 150 mg once daily. This medication should be avoided in patients with renal impairment and who have an increased risk of hyperkalemia. This is used as adjunctive therapy for women who reported HS flare with the menstrual cycle. Other hormonal agents such as combined oral contraceptive pills, progestogen-only pills, and other medications are based on very limited evidence. In addition, dapson and cyclosporine have little evidence to support their use in the treatment of HS. A report with oral dapsone (N=24) showed that 62 percent of patients did not show improvement. Oral cyclosporine use has shown that only two patients responded among a study of 18 patients with HS.

Ertapenem is an intravenous antibiotic that can be used in a severe flare and when oral antibiotics are entirely ineffective. It can also be considered in the interim when switching a patient from one biologic medication to another one. This antibiotic is considered a rescue medication, which is meant to deliver short-term relief of symptoms. It is administered at 1 gm IV daily for six weeks and has a high efficacy.

Laser treatment is an option in patients in Hurley Stage II and III. The 1064nm Neodymium-doped yttrium aluminum garnet (ND-YAG) lasers have been shown to have the best efficacy, with four treatments at four-week intervals. This laser is non-ablative, which means it does not damage the outer layer of the skin. Settings used for Fitzpatrick skin types I to III (Table 2) were typically 35 to 50 J/cm2, a spot size of 10 mm, and 10 ms pulse duration. Fitzpatrick skin types IV to VI (Table 2) were used 25 to 240 J/cm2 and 20ms pulse duration. Alternative lasers, such as intense pulsed light (IPL), alexandrite, and diode, have had disappointing results.

Photodynamic therapy (PDT) using either topical or intraleisonal 5–aminolevulinic acid (ALA) can induce bacterial cell death because of the photosensitizing topical chemical applied. The PDT treatment has not been shown to be effective. The penetration of the ALA into the HS lesions is the central issue that has led to the more specific intraleisonal application of the ALA technique to obtain better results. A study showed some increased efficacy using the intraleisonal technique, but the sample size was small. CO2 lasers are typically reserved for excising lesions, and fractionated CO2 lasers can reduce scarring.
Table 2. Fitzpatrick Skin Types\textsuperscript{11}

<table>
<thead>
<tr>
<th>Fitzpatrick Type</th>
<th>Appearance/ Features</th>
<th>Tanning Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Pale white skin to very fair skin</td>
<td>Always burns, never tans</td>
</tr>
<tr>
<td></td>
<td>Light-colored eyes Red or blonde hair</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May have freckles</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>Fair skin</td>
<td>Usually burns, tans with difficulty</td>
</tr>
<tr>
<td></td>
<td>Light-colored eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Light hair</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>White, light brown skin</td>
<td>Sometimes burns, gradually tans</td>
</tr>
<tr>
<td></td>
<td>Eye color varies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium to dark hair</td>
<td></td>
</tr>
<tr>
<td>Type IV</td>
<td>Light brown skin</td>
<td>Minimally burns easily</td>
</tr>
<tr>
<td></td>
<td>Dark eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dark hair</td>
<td></td>
</tr>
<tr>
<td>Type V</td>
<td>Brown skin</td>
<td>Rarely burns, tans easily and quickly</td>
</tr>
<tr>
<td></td>
<td>Dark eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dark hair</td>
<td></td>
</tr>
<tr>
<td>Type VI</td>
<td>Dark brown or black skin</td>
<td>Never burns, tans easily and darkly pigmented</td>
</tr>
<tr>
<td></td>
<td>Dark eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dark hair</td>
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</tbody>
</table>

CO2 lasers are considered ablative lasers, which damage the outer layer of skin, producing new collagen. Although CO2 laser excision has provided some favorable results, there is limited evidence to support the efficacy.\textsuperscript{3}

Hurley Stage III. Patients with refractory HS or moderate to severe disease are candidates for a biologic agent. Biologic agents already in use for other diseases have shown promise for HS. If a patient has an acute flare, the deroofing of new or small chronic lesions is advised, oral antibiotic therapy may be initiated, and a short course of oral prednisone, pulse-dosed, or in multiweek taper depending on severity, may be used in selected cases.

Currently, adalimumab is the only biologic with United States Food and Drug Administration (FDA) approval for the treatment of HS since 2015. Adalimumab is a TNF-\alpha inhibitor. The complexity of the interactions of TNF-\alpha and the relationship to HS is not entirely understood, but if TNF-\alpha levels are elevated in the skin, it does correspond to the severity of HS disease.\textsuperscript{3,10} The TNF-\alpha inhibitor binds with TNF-\alpha, which inhibits its interaction and proinflammatory effects in the body.\textsuperscript{3,5}

Adalimumab dosing is 40 milligrams weekly. The Pioneeer II study results revealed a 59-percent response rate, and the weekly dosing of adalimumab has better results in maintaining HS than switching to every other week dosing.\textsuperscript{6,7} In the non-responders’ group at 12 weeks, 40 percent were subsequently responding and continued to respond to treatment by 56 weeks.\textsuperscript{6,7} Adalimumab does show significant improvement in patients’ quality of life (QoL) scores with continued treatment in Dermatology Life Quality Index (DLQI) scores.\textsuperscript{12} DLQI is a simple patient self-assessment test that can be done in-office consisting of 10 questions regarding the skin and how it has affected the patient’s life over the past week.\textsuperscript{10}

Infliximab is another TNF-\alpha inhibitor that can be considered but is not FDA-approved. However, in the event of failure to adalimumab, infliximab may be effective.\textsuperscript{6,7} Infliximab is administered as an IV infusion and is started with an induction regimen followed by eight-week intervals.\textsuperscript{6,7}

Anakinra is an interleukin antagonist that completely inhibits IL-1A and IL-1B from binding to the IL-1A receptor. As a result, IL-1B levels are higher in lesional and perilesional skin of HS patients.\textsuperscript{5–7} Several studies demonstrate the effectiveness of anakinra; however, one reported that 100 mg daily for 12 weeks effectively reduces HS and can be tried if a patient fails the TNF-\alpha inhibitor class.\textsuperscript{7} Using this medication for HS is considered off-label use because it has no FDA approval for the indication of treatment in HS. While the approval for off-label medications is cost-prohibitive and sometimes challenging, the American Academy of Dermatology (AAD) has prior authorizations templates to help navigate a successful appeal.

The IL-12 and IL-23 inhibitor ustekinumab has also shown efficacy in patients with HS. IL-12 and IL-23 are expressed in HS patients because of activated macrophages.\textsuperscript{6} Ustekinumab is a monoclonal antibody and binds to the subunit p40 of both IL-12 and IL-23.\textsuperscript{6,7} A self-administered injection, 45–90 mg, is given at weeks 0, 4, and then every 12 weeks and showed improvement in the group of 17 subjects with HS.\textsuperscript{5–7} The study was small, and this drug should also only be considered if the TNF-\alpha inhibitor class fails.\textsuperscript{5,6} Ustekinumab is not FDA approved for the treatment of HS. Two other TNF-\alpha inhibitors, etanercept and golimumab, currently lack the evidence to support their use as options in treating HS.\textsuperscript{6}

Hurley Stage III patients would be candidates for wide local excision of an HS affected area. Overall, surgical treatment is best considered when all other treatment modalities have failed. It should be noted that most studies are conducted on patients that have had severe Stage III disease for decades with very little prior treatment success.\textsuperscript{13} The studies supporting surgery are uncontrolled retrospective reports and show recurrence rates of HS lesions anywhere from 24.4 percent to as high as 100 percent.\textsuperscript{6} Some studies and QoL results show that wide local excision with
at least 2 cm margins result in positive improvement for patients with severe HS.\textsuperscript{13} A meta-analysis reviewed the type of closure and recurrence rate and revealed that 15 percent recurred with primary closure, eight percent recurred with skin flaps, and six percent recurred with skin grafts.\textsuperscript{7} The most common surgical complications were pain and scarring, some extensive enough to restrict mobility.\textsuperscript{13} These procedures are generally performed by general surgeons and may or may not be outpatient. Pain is typically post-procedure and is manageable with oral medication if necessary, and scarring ranges from keloid formation to contractions. It is generally accepted that surgery does not change the course of the disease; recurrence and new lesions are not unexpected.\textsuperscript{4}

COMORBIDITIES OF HS

Patients with HS often have many other physical or psychological comorbidities, and a thorough review of symptoms and appropriate routine screening are essential components of the overall care of these patients.\textsuperscript{14} Some comorbid skin conditions can be elucidated from the skin exam, while other comorbidities can be revealed during a review of systems (ROS).\textsuperscript{14} The ROS can help prioritize referrals to other specialists as some specific screening exams are not in the scope of dermatology providers.\textsuperscript{14}

Underlying systemic inflammation appears to be the common factor in several comorbidities that have been associated with HS. These include arthropathies, dyslipidemia, hypertension, metabolic syndrome, obesity, thyroid disorder, PCOS, psoriasis, type 2 diabetes mellitus, and squamous cell skin cancer of the HS-affected skin.\textsuperscript{3,6}

Screening is advised in patients who exhibit signs or symptoms related to androgen excess, diabetes, hyperlipidemia, hypertension, menstrual irregularity, and obesity because these are the highest risk comorbidities found in patients with HS.\textsuperscript{3,6} Psychiatric disorders such as anxiety and depression should also be addressed. HS can cause stress or anxiety in patients. An HS flare and the resulting symptoms (malodor, pruritus) can interfere with their everyday activities or negatively impact their work, potentially leading to depression.\textsuperscript{12} Depression can be screened using the Patient Health Questionnaire-\textsuperscript{2,9,15} The questionnaire consists of two questions and can help identify a patient that may need a referral for additional counseling.\textsuperscript{9,15} The quick assessment can be easily administered by a medical assistant and reviewed during the initial visit.\textsuperscript{9}

There is an increased proinflammatory response in patients with HS, and the prevalence of obesity or being overweight among the patient population with HS is 75 percent.\textsuperscript{6,16,17} Patients with HS lesions with high body mass index (BMI) had a higher Hurley stage and more anatomical sites that have HS when compared to those with low BMI.\textsuperscript{3} Several studies on weight loss, including bariatric surgery, have shown a reduction in symptoms, but evidence of weight loss being beneficial overall to HS is conflicting.\textsuperscript{5,16,17} Nutritional studies and diet modifications are also routinely investigated. A report showed that avoidance of some foods such as yeast and sugars could lead to a reduction in HS lesions.\textsuperscript{18} Patients are often looking for guidance in this complicated area, and referral to a nutritionist may be best; however, support to improve dietary intake should be provided.

Squamous cell carcinoma of chronically involved HS areas can evolve, particularly on the perineum or buttocks, and therefore, monitoring for this in patients with HS is essential.\textsuperscript{5,6,19} Tobacco use is associated with HS. Nicotine stimulates T-helper17 cells, stimulates TNF release, and affects the cutaneous microbiome.\textsuperscript{20} Tobacco and, therefore, smoking has long been linked to HS.\textsuperscript{21–23} Estimates show that up to 15 percent of patients with HS have smoked, and up to 75 percent still smoke.\textsuperscript{6,7} Research has failed to demonstrate a correlation, although tobacco cessation for additional health reasons has been identified and should be encouraged.\textsuperscript{21–23} Hypertension is often associated with HS. Tobacco use and obesity are independent risk factors for hypertension, and both are comorbidities associated with HS.\textsuperscript{20} Cerebrovascular accident, myocardial infarction, and cardiovascular death are all associated with a higher incidence in patients with HS, and although this association is unclear, chronic inflammation is suspected.\textsuperscript{20}

CONCLUSION

HS is a chronic and relapsing skin disorder. A significant increase in awareness of HS and new understanding of its proposed pathophysiology has helped providers with what was once a challenging diagnosis. This information has stimulated the development of new therapies that may improve patients’ overall quality of life. Effectively managing a patient from Hurley Stage I to Hurley Stage III with efficiency is the goal. Patients will benefit from a structured, Hurley stage-treatment approach, but the treatment that is decided upon is ultimately chosen after careful discussion between the provider and the patient.\textsuperscript{2}

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DISCLOSURES

The author has disclosed no potential conflicts of interest, financial or otherwise, relating to the content of this article.
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