Obstacles to Early Diagnosis and Treatment of Hidradenitis Suppurativa: Current Perspectives on Improving Clinical Management

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Abstract: Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that can progress to significant tunnels and scars that affect quality of life, especially if diagnosis and treatment are delayed. Average delay after initial presentation of HS symptoms can range from 3 to 10 years in adults and 1 to 2 years in children. Factors associated with diagnostic delay include female gender, non-white race, and greater disease severity at diagnosis. Contributing factors include misdiagnoses, difficulty accessing a dermatologist, hesitation in seeking care due to the stigmatizing nature of the disease, and lack of awareness among providers and patients. While efforts to increase awareness include academic talks at conferences and by foundations geared toward HS, social media offers the opportunity to reach young audiences. Many patients report dissatisfaction with their HS treatments. Better understanding of HS pathophysiology and implementation of clinically focused phenotypes and endotypes can lead to development of more targeted and efficacious therapies. FDA approval of medications for HS beyond adalimumab will increase access to a wider selection of therapies, and implementation of therapeutic drug monitoring may maximize the use of biologics for HS.

Keywords: hidradenitis suppurativa, acne inversa, diagnosis, delayed diagnosis, therapeutics, time-to-treatment

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by recurrent painful nodules and abscesses that can progress to draining tunnels and scars, affecting an estimated 1% of the population.1 In Europe and North America, HS has a 3:1 predilection in females compared to males, and symptom onset typically occurs in early adulthood.1 HS can significantly impair an individual’s quality of life by negatively impacting patients’ interpersonal relationships, reducing the ability of patients to maintain employment, and contributing to the high prevalence of depression and anxiety in this population.2–4 Further, being in a chronic state of inflammation has been shown to increase risk for other comorbidities, including cardiovascular conditions, and possibly cancers, such as squamous cell carcinoma and Hodgkin lymphoma.5–7 These factors make early diagnosis and effective treatment critical.

Prior to 2015, there were few effective therapies for HS, and surgery was the primary treatment option employed for most patients.8 Adalimumab was approved by the Food and Drug Administration (FDA) for moderate-to-severe HS in 2015.9,10 Medical management is a rapidly growing area of research with multiple pharmaceutical companies pursuing Phase 2 and 3 studies.11,12 However, patients with HS are now mostly likely to benefit from a combination of medical and surgical management with a recent study showing better outcomes for surgery in conjunction with adalimumab compared to adalimumab alone.13

This review seeks to summarize the current state of delays in diagnosis and treatment of HS and to explore the associated obstacles and potential solutions.
Barriers to HS Diagnosis
Pathogenesis and Diagnosis
Apocrine glands were originally hypothesized to be the primary driver of HS, which led to the misnomer “hidradenitis” meaning “inflammation of the sweat gland.” This hypothesis came about in the 1800s by the French surgeon, Aristide Verneuil, and was seemingly confirmed in 1955 from experiments by Shelley and Cahn.8,14 Later studies identified the hair follicle as the primary structure involved and an effort to rename HS to “acne inversa” was made.8 Currently, experts believe follicular hyperkeratosis and dilation followed by follicular rupture and an inflammatory response are the main events leading to disease.1 However, many aspects of the pathophysiology of HS remain unclear.

The diagnosis of hidradenitis suppurativa is made clinically based on history and presentation of recurrent typical lesions (inflammatory nodules, abscesses, comedones, scarring, and/or tunnels/sinus tracts) predominantly in the intertriginous (ie, axillae, inframammary, groin, buttocks, etc.) areas.15 The differential diagnosis includes infection, folliculitis, furuncles (“boils”), acne vulgaris, inflamed epidermal cysts, and cutaneous Crohn’s disease.16 HS disease severity is often graded using the Hurley surgical staging system, which ranges from mild (stage I) to severe (stage III).15,17

Diagnostic Delay in HS
Across eleven studies, the diagnosis of HS after initial presentation of symptoms ranged from 3 to 10 years with most studies finding a delay of 6 to 10 years.18–28 Two studies that focused only on patients diagnosed prior to 2013 found the average delay also around 7 years.18,19 Recent studies from 2017 to 2020 showed similar findings, with an average delay of 10 years, indicating that diagnostic delay remains an ongoing barrier to care for patients with HS.15–22

In the pediatric population, delay in diagnosis has been shorter. Two studies focusing on pediatric HS reported diagnostic delays of 1–2 years.29,30 The average onset of symptoms was 14 and 12.6 years old, and both studies reported a considerable proportion of patients with Hurley II/III disease (64% and 40%, respectively).29,30 In a study of 481 pediatric patients, Liy-Wong et al found that 48% had scarring evident at their initial dermatologic assessment.31 Due to the progressive nature of HS, timely diagnosis is paramount in improving patient quality of life.32 Even short delays in diagnosis can lead to irreversible scarring.

Beyond worsening morbidity in patients, diagnostic delay may also lead to greater costs to the healthcare system. A 2014 study that included over 16,000 patients with HS found inpatient care to be the largest component of their healthcare spending with almost 16% hospitalized over a 3-year period and over a quarter were seen in the emergency department.33 Earlier diagnosis and implementation of proper maintenance therapy would likely reduce utilization of these high-cost settings and shift the focus to outpatient management.34 Additionally, prolonged delays in diagnosis have been suggested to increase the likelihood of missing more days of work which can lead to loss wages in patients.3

Factors Associated with Diagnostic Delay
Factors associated with diagnostic delay include non-white race, greater disease severity, and higher number of comorbidities.20,23 While HS predominantly affects women, a global survey study found that women were more likely than men to experience a diagnostic delay of over two years. In both adult and pediatric HS patients, severe disease was associated with greater diagnostic delay. This differs from other skin disorders like psoriasis, in which patients with severe disease tend to be diagnosed earlier.18 Given the intimate areas of the body involved, patients with severe disease may be less willing to disclose their symptoms or seek medical care due to feelings of shame or fear.

In pediatric patients, factors associated with diagnostic delay include higher body mass indexes, greater disease severity, multiple affected body sites, and earlier age of onset (≤14 years). Notably, significantly more patients with earlier ages of onset (≤14 years) had involvement of their genital region.29 Fear and embarrassment may prevent pediatric patients from disclosing their symptoms to guardians or medical providers, while health-care providers may also be reluctant to conduct thorough physical examinations due to concerns of causing patient discomfort.
Misdiagnosis of HS

Patients with HS, on average, see more than three different physicians and undergo more than three misdiagnoses before finally receiving the correct diagnosis of HS, which is commonly made by a dermatologist.\cite{20,21} HS is commonly confused for conditions such as infection, folliculitis, and furuncles (“boils”).\cite{16} Due to early but incorrect hypotheses that HS was caused by an infectious process, providers may recommend improved hygiene practices to their patients. This flawed understanding of HS pathogenesis can not only delay proper diagnosis and treatment, but also cause patients to feel stigmatized, leading to a breakdown in trust between the patient and provider.

Need for Increased Awareness Among Providers

While HS is often primarily managed by dermatology once the diagnosis has been established, it is vital for non-dermatologic providers to be aware of this condition. Access to dermatology is often complicated by scarcity of providers, long wait times, and limitations by patient insurance.\cite{22,35} Patients frequently present to providers in other specialties, including family medicine, internal medicine, obstetrics and gynecology (OBGYN), pediatric, and emergency medicine. Providers in urgent care centers and emergency departments may frequently encounter HS flares, particularly before the HS diagnosis is made. HS also requires a multidisciplinary approach given its association with comorbidities including metabolic syndrome, type II diabetes, polycystic ovarian syndrome (PCOS), mental health disorders, inflammatory bowel disease (IBD), and arthropathies.\cite{1} Therefore, providers of many different specialties should be knowledgeable about HS in order to provide timely diagnoses and optimal treatments.

In a 2021 survey of 211 family medicine physicians, only 23.7% reported feeling confident in diagnosing HS. Furthermore, 63% defined HS as an infectious process of apocrine glands, highlighting the flawed perception that HS is caused by infection.\cite{36} Medical journals are valuable resources for physicians to expand their knowledge and remain updated, yet in HS, most recent publications are authored by dermatologists. A literature search for HS publications from January 2000 – February 2020 found that 73.3% were published in dermatology journals. In contrast, from 2013 to 2019, three or fewer HS-related articles were published in OBGYN, family medicine, pediatric, and emergency medicine journals annually.\cite{37} Thus, disseminating information about HS to non-dermatologists is crucial, and will require targeted outreach measures such as publishing in non-dermatology journals or presenting at non-dermatology conferences.

Within dermatology, significant strides have been made towards increasing awareness, education, and research pertaining to HS. A PubMed search for “hidradenitis suppurativa” in March 2023 illustrated a massive increase in HS research with the number of publications from January to March 2023 already surpassing the annual HS publications in 2015 or any year prior.\cite{38} As noted above, most of these publications are in dermatology journals, so effort is still needed to educate other specialties on how to recognize and initiate treatment for HS. This year’s annual meeting of the American Academy of Dermatology dedicated over 10 hours of educational sessions to HS, focusing on medical and surgical management.\cite{39} Furthermore, foundations focused on HS advocacy, education, and research have formed internationally. One of the main organizations in the US, the Hidradenitis Suppurativa Foundation, educates patients and advanced practice providers through dedicated meetings such as “Symposium on Hidradenitis Suppurativa Advances.”\cite{40}

Shame and Stigmatization in HS Patients

Patients with HS have reported feelings of shame, unworthiness, and being unlovable, especially with more advanced disease.\cite{41} These feelings are encompassed by the term “internalized stigma”, which is the acceptance of negative attitudes and stereotypes of society regarding a person’s illness. Factors predictive of high internalized stigma among HS patients include obesity, low educational level, low income level, and genital involvement.\cite{42} Many patients have described their symptoms as “embarrassing” or “repulsive”, and often go to great lengths to hide them from others.\cite{42} In our HS specialty clinic, many patients are unsure if they have a family history of HS stating their family does not discuss such intimate or personal symptoms.

In general, patients with stigmatized health conditions are less likely to seek medical care.\cite{41} This can be exacerbated when patients feel blamed for their condition. Early hypotheses of HS, mixed with lack of general public knowledge,
perpetuated misconceptions that HS was caused by poor hygiene, large body weight, and smoking. As recently as 2011, two German dermatologists attempted to rename HS as “smoker’s boils” due to the high prevalence of smoking among patients with HS. Although smoking and lifestyle changes should be addressed during visits, providers should recognize that management of HS, particularly more severe disease, with lifestyle choices alone is usually inadequate. Thus, providers should be careful to not imply that HS is a result of lifestyle choices alone.

Opportunity for Social Media
Support groups can provide a crucial connection for patients feeling similar life circumstances. By participating in these groups, patients can reduce feelings of loneliness, exchange knowledge, and shift their outlook on living with their condition. However, most patients only join these groups once they receive a diagnosis or suspect they have the condition. Social media has enabled patients to seek information anonymously about symptoms they may feel too embarrassed to discuss with a health-care provider face-to-face, and has been particularly effective in spreading awareness about less well-known conditions such as HS. For example, a two-year HS awareness campaign in Italy utilized many outlets, including social media, to disseminate information about the condition, resulting in over 500 new HS diagnoses.

Social media platforms, such as Facebook, Twitter, Instagram, and TikTok, also serve as communities from which patients seek education related to their disease. Observations from the largest HS support group in 2017–2018, consisting of almost 13,000 members, found that over half of the posts were requests for information, predominantly about lifestyle changes, symptom management, and experiences with medications. In 2020, videos related to HS on TikTok received over 12 million views. In our office, we have observed many patients who have self-diagnosed based on social media posts and then self-referred to our HS specialty clinic. However, it is important to note that social media can also facilitate the spread of misinformation, and many health-related claims are based on anecdotes that may lack evidence. Rather than discouraging HS providers from participating in social media, experts should be encouraged to disseminate accurate and up-to-date information on these platforms. This may increase awareness, reduce stigma, and ultimately lead to faster diagnosis and treatment of HS.

Barriers to HS Treatment
Overview of Treatment Options
Treatment strategies for HS include lifestyle modification, medical therapies including biologics, and procedural interventions. The current North American clinical management guidelines for hidradenitis suppurativa, last updated in 2019, details recommendations based on Hurley stage. Hurley stage I consists of recurrent nodules and/or abscesses with minimal scarring and no sinus tract formation. Hurley stage II is characterized by recurrent inflammatory nodules and/or abscesses, often with worsened scarring, and formation of sinus tracts separated by normal appearing skin in an anatomic area. Hurley stage III has more extensive sinus tract formation than Hurley stage II that affects an entire anatomic area(s).

Acute flares can be managed with warm compresses, oral and intravenous antibiotics, short-term oral steroids, intralesional steroids, and incision and drainage. Antibiotics used for acute flares have limited evidence but may include tetracyclines, clindamycin, rifampin, metronidazole, moxifloxacin, dapsone, or IV ertapenem. IV ertapenem can be highly effective and useful while initiating or optimizing maintenance therapy, and the risks of prolonged broad spectrum antibiotic use should be carefully considered for courses beyond 6 weeks. These treatments may offer rapid relief but are associated with high rates of recurrence. Topical therapies, which may be used as monotherapy in mild disease and adjunctive therapy in Hurley stage II and III, include topical resorcinol, topical chlorhexidine, and topical clindamycin (often combined with benzoyl peroxide to prevent microbial resistance). Maintenance therapy includes oral antibiotics (tetracyclines, rifampin + clindamycin), hormonal treatments (spironolactone, oral contraceptive pills, and finasteride), retinoids, and biologics.

TNF-α and interleukin-17 (IL-17) inhibitors have shown efficacy for moderate-to-severe HS. In clinical trials, the primary outcome is typically Hidradenitis Suppurativa Clinical Response (HiSCR50), defined by a 50% decrease in
abscess and inflammatory nodule count with no increase in the number of abscesses or draining fistulas.\textsuperscript{53} Adalimumab remains the only FDA-approved treatment for moderate to severe HS.\textsuperscript{9,10} In two landmark Phase 3 clinical trials, 42\% and 59\% of patients treated with adalimumab achieved HiSCR50.\textsuperscript{9} Infliximab dosed 7.5–10mg/kg every 4 to 8 weeks is also frequently used off-label for moderate to severe HS.\textsuperscript{54} IL-17 inhibitors have also shown promising data in clinical trials, and will likely be approved for HS in the imminent future. In phase 3 clinical trials, secukinumab, an IL-17A inhibitor, led to HiSCR50 in 42\% and 46\%, and bimekizumab, an IL-17A and F inhibitor approved in Europe, led to HiSCR50 in 50\% and 61\% of HS patients.\textsuperscript{51,52} Multiple other phase 2 HS clinical trials showing positive results have also been completed for sonelokimab (IL-A/F inhibitor), izokibep (IL-17A inhibitor), and povorcitinib (janus kinase 1 inhibitor), and eltrekibart (monoclonal antibody that binds to the ligands signaling CXCR1 and CXCR2).\textsuperscript{11} While HiSCR50 remains the historical primary endpoint in many trials, fifty percent improvement in disease may not be significant for all patients and can still represent a significant disease burden. Some clinical trials are now utilizing 75\% and 90\% improvement (HiSCR75 and HiSCR90, respectively) as a primary and/or secondary endpoint, increasing the efficacy bar for clinical trials with the ultimate goal of ideally identifying treatments that will demonstrate both a greater depth of response as well as a response in a greater proportion of patients.\textsuperscript{52,55}

Excisions and deroofings should also be considered for Hurley stages II or III when sinus tracts are present, or for localized, recalcitrant lesions.\textsuperscript{10} Surgical or laser procedures can be performed without having to stop biologic therapy. Notably, the SHARPS study found that there was no need to interrupt adalimumab treatment prior to surgery.\textsuperscript{56} In this Phase 4 study, subjects with HS were randomized to the FDA approved dosing of adalimumab for HS versus placebo. The primary outcome was HiSCR50 at week 12, and subjects underwent surgery between weeks 12–14 and were followed for 10 additional weeks. There was no increased risk of postoperative wound infections, complications, or hemorrhage in the adalimumab group.\textsuperscript{59} As previously mentioned, a randomized controlled trial comparing adalimumab plus surgery to adalimumab alone found greater improvements in quality of life and clinical effectiveness for the combined therapies.\textsuperscript{13} Deroofings and localized excisions can be performed in outpatient settings for smaller areas. For larger areas, particularly those requiring flaps or grafts, plastic or general surgery is typically pursued. Laser hair removal and marsupialization with ablative lasers can also benefit some patients with HS.\textsuperscript{10}

### Treatment of HS-Related Comorbidities

Beyond medical management of HS, involvement by other specialties for care HS-associated comorbidities is crucial.\textsuperscript{1,10,15,57} Smoking cessation specialists and nutritionists can be beneficial to mitigate the impact of two common HS flare triggers, smoking and obesity. OBGNs and endocrinologists are necessary to address PCOS and fertility issues commonly seen in female patients with HS. When IBD or inflammatory arthropathies are suspected, gastroenterologists and rheumatologists, respectively, are necessary. Mental health disorders including depression and anxiety are extremely common in HS, making psychiatrists and psychologists important parts of the care team. Many patients experience chronic pain related to their disease or comorbidities requiring pain management specialists. For Hurley stage II and III patients, access to general or plastic surgeons familiar with HS is crucial.\textsuperscript{1,10,15,57} HS is a life-long, often debilitating condition that can affect many aspects of a patient’s life. Palliative care specialists are the most equipped in handling situations such as these and should be considered.\textsuperscript{58}

### Barriers to HS Treatments

The vast majority of publications regarding HS treatments from 2008 to 2018 were case reports and case series, and more high-quality evidence in the form of clinical trials and prospective studies are still needed.\textsuperscript{12} Greater consensus is also needed for many treatments. Hendricks et al compared HS management guidelines as of 2019 among nine different organizations from across the world and found only first-line therapies such as topical clindamycin, oral tetracyclines, combination clindamycin and rifampin therapy, adalimumab, and wide local excisions had consensus. Meanwhile, second- and third-line therapies demonstrated more discrepancy.\textsuperscript{59}

This lack of consensus may be related to the heterogeneous nature of HS and the low efficacy of many of the currently utilized HS therapies. Differences in dominant lesion types (inflammatory nodules, comedones, draining fistulas, or abscesses) may be associated with different responses to treatments.\textsuperscript{15} There have been multiple attempts
to classify HS into clinical subtypes, but none has been validated for therapeutic use. HS clinical trials have not yet incorporated phenotypes, so it is unknown which subset of patients respond better to medications. Clinically relevant phenotypes or endotypes, genetic testing, and cytokine profiling may further our understanding of HS and allow for tailoring of individualized treatments.

The pathophysiology of HS is also complicated and multifactorial with much still unknown, including the pattern of disease progression. Translational research has implicated IL-1β, TNF-α, IL-10, and IL-17 pathways in HS skin. The most successful clinical trials to date target some of these aspects of the immune system; however, many of these trials also exclude patients who have new onset or acute disease within the past 6 to 12 months, and the average patient in HS clinical trials tends to have disease for greater than 5 years. Further elucidation of the underlying pathophysiology HS will hopefully lead to advancements in therapies and inclusion of patients in clinical trials with earlier disease.

Even with the availability of new drugs, a delay in starting biologic therapies in patients with moderate or severe HS may still exist. This may be due to lack of HS providers willing to prescribe these drugs or patient hesitation to take these medications. In a survey of almost 2000 HS patients, Garg et al found that 46% reported dissatisfaction with their current treatment. The most common reason for dissatisfaction was perceived lack of efficacy (43%). However, only 21% were prescribed biologic therapy, while 86% had been prescribed oral antibiotics, and 70% had received incision and drainages. Ring et al reported a mean of 15 years from time of first systemic therapy to first biologic therapy, and 21% of patients received 5 different treatments prior to starting a biologic. As biosimilar adalimumab becomes available, potentially lowering the price of therapy, and multiple and potentially more efficacious biologics are approved for treatment of HS, we may see earlier and greater utilization of biologic therapy. Therapeutic delay of more than 10 years has also been correlated with lack of response to adalimumab, but it is still unknown if earlier treatment can halt the disease process and prevent scarring or disfiguring disease.

Summary of Potential Solutions
Reducing delay in diagnosis and treatment of patients with HS requires a multi-pronged approach focused on continued research into efficacious treatments and the pathophysiology of the disease and increasing awareness and education among both providers – dermatologists and non-dermatologists – and the public.

Increasing the efficacy and quality of evidence of the available treatment options is imperative. We have made great strides over the past three years in the clinical development of medications for HS. Additionally, more clinical trials are including outcome measures with higher bars of improvement such as HiSCR75 and HiSCR90, and this will need to become the standard going forward. Future clinical trials also need to consider expanding to include pediatric populations as well as those with acute onset disease, and eventually, head-to-head trials comparing medications must be performed.

As this is a very heterogeneous disease, specific treatments based on HS clinical morphology, comorbidities, or other disease-specific characteristics will also improve dermatologists and dermatology providers’ ability to prescribe the best first-line therapies. Establishment of HS phenotypes and treatment response by phenotype will be essential as patients with mild follicular or folliculonodular disease may be better suited to certain therapies than those with severe inflammatory or infiltrative disease. Further, an emphasis on translational research will allow better understanding of the inciting factors and progression of HS that may potentially differ based on a patient’s individual phenotype or genotype.

For dermatologists and dermatology providers who will be the primary specialist prescribing specialty medications for HS, continued education about the rapid evolving treatment landscape is imperative for providers to feel comfortable treating this disease. Formal education of HS is currently part of dermatology continuing medical education conferences and most residency training programs, and published research related to HS continues to increase in dermatology journals. Education about the disease and treatment options also needs to occur in other non-dermatology specialties, including internal medicine, family medicine, emergency medicine, OB/GYN, and pediatrics. As dermatologists, we should consider providing didactic lectures to our colleagues in other specialties through local presentations at scheduled educational conferences that specifically focus on increasing awareness of the disease diagnosis, treatment for flares, and steps for referral to specialists. Improving knowledge amongst providers will increase our HS patients’ trust in medical care overall.
Another strategy to increase awareness and education among providers and the public is an increased emphasis on social media platforms such as TikTok, Instagram, and Facebook. Stigmatization and embarrassment are both likely major contributors to patients avoiding care when their symptoms first arise. Normalization through communities on social media and a larger presence of providers who can explain not only the current treatment strategies available but also emphasize the pipeline of treatments coming soon will drive new patients and those previously disappointed about what medicine offered them in the past to seek care.

Conclusion
The diagnosis of HS is often delayed by 3 to 12 years, and patients, particularly those who are non-white, female, or have more severe symptoms, may experience 3 to 4 misdiagnoses before receiving an accurate diagnosis. Ongoing efforts to increase HS awareness and education include formation of support groups and HS-related foundations, but there is still more work to be done. It is crucial to disseminate up-to-date information to all health-care providers who may encounter HS patients to ensure timely diagnosis and appropriate treatment. Additionally, more research is needed to better understand the pathogenesis of HS and develop more effective therapeutic options. By addressing these challenges, we can improve the quality of life for individuals living with HS and reduce the burden of this chronic disease.

Disclosure
This research received no financial support. Each author’s financial/conflict of interests are below.

Snyder CL: No conflicts of interests to disclose.
Chen SX: Dr. Chen is an investigator for Novartis, Moonlake, Prometheus, and UCB.
Porter ML: Dr. Porter is a consultant and/or investigator for AbbVie, Bristol Meyers Squibb, Janssen, Eli Lilly, Moonlake, Novartis, Pfizer, Trifecta Clinical (on behalf of acelyrin), UCB, Arista, Regeneron, Innovoderm, Bayer, Prometheus, and Incyte. Dr. Porter reports grants from AbbVie, Anaptyx Bio, Arista, Bayer, Eli Lilly, Janssen, Pfizer, Prometheus Labs, Regeneron and SonomaBio, outside the submitted work. Also, royalties paid from BIDMC from HS training modules. The authors report no other conflicts of interest in this work.

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