



# The Treatment of Genitoperineal Hidradenitis Suppurativa: A Review of the Literature

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Hidradenitis suppurativa is a chronic inflammatory condition affecting the axilla, genitals, perineum, and perianal regions. The pathophysiology of hidradenitis suppurativa is complex and requires a multidisciplinary approach to treatment involving medical and surgical management when indicated. We describe our multidisciplinary protocol for treatment, which includes rheumatology-monitored immunotherapy, medical management, wide surgical resection, wound care, and reconstruction. The multidisciplinary care team includes rheumatology, wound care, and reconstructive urologic surgery. Surgical management includes wide local surgical resection, negative pressure dressing, delayed reconstruction, and perioperative immunotherapy. Multimodal treatment with surgical, medical, wound, and immunotherapy care is vital to successful treatment. *UROLOGY* 124: 1–5, 2019. © 2018 Elsevier Inc.

**H**idradenitis suppurativa (HS) is a chronic inflammatory condition affecting the axilla, genitals, perineum, and perianal regions (Fig. 1). Although HS is a female predominant diagnosis, extra-axillary manifestations are more commonly found in men.<sup>1</sup> HS can manifest with abscesses, sinus tract formation, and scarring resulting in significant disfigurement as well as pain. HS patients often suffer from psychological consequences of chronic pain and embarrassment from skin lesions and chronic wounds. In the case of genitoperineal HS, patients may endure other unique physical and psychosocial consequences due to the affliction of sexual organs.<sup>2</sup> The pathophysiology of HS is complex and not completely understood, as it is now thought to result from immune dysregulation in conjunction with other predisposing risk factors. Given this complexity, treatment often requires a multidisciplinary approach involving combined medical and surgical management.

There are currently 22 National Institutes of Health (NIH) clinical trials; however, there is a paucity of evidence on the topic of genitoperineal HS. We sought to review the literature using MEDLINE, Cochrane, and EMBASE in order to characterize the current and novel data regarding experiences with the treatment of genitoperineal HS.

## BACKGROUND

HS is characterized by cyclic inflammation of follicular ducts as a result of obstruction from excessive keratinocytes.

Immune dysregulation is hypothesized to foster this characteristic pathology.<sup>3,4</sup> The initial mechanism that lays the foundation for inflammation to develop is not dissimilar from that of acne or abscess formation; however, hyperkeratosis is a unique histologic finding in HS.<sup>3,4</sup> In HS, follicular ducts fail to extend to and open at the skin's surface, thus spreading in a subcutaneous fashion.<sup>3,4</sup> Although a discrete etiology has not been identified, many risk factors are associated with and the progression of HS, including family history, smoking, hormonal abnormalities, obesity, and Crohn's disease.<sup>3,4</sup>

The diagnosis of HS is based on the clinical history differentiated by the recurring nature with which this pathology occurs. Additionally, classification systems have been developed to better describe and objectively define disease severity. The Hurley classification, ranging from Stage I to III, categorizes the progression of disease by the description of pathologic healing.<sup>3,4</sup> Stage I is defined by abscess formation (single or multiple), without sinus tract formation or cicatrization. Stage II progresses to recurrent abscess with evidence of tract formation and cicatrization. Stage III reflects almost diffuse involvement or multiple interconnected abscesses and sinus tracts across an entire region.<sup>3,4</sup> Although it is based purely on visual manifestation of disease, the Hurley staging system may help in defining severity and thus aid in determining treatment modality. Other factors affecting treatment choice include the physical and psychosocial implications of the body region affected. As such, additional tools (the Sartorius score and Dermatology Quality of Life Index ) are available to further describe region and psychosocial impact of the disease.<sup>5,6</sup>

Besides the potential disfigurement and dysfunction resulting from longstanding untreated HS, patients are also at risk of fistulas, lymphedema, and malignancy.<sup>7</sup> Some physicians

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**Figure 1.** Genitoperineal hidradenitis suppurativa. (Color version available online.)

feel that HS presenting in extra-axillary sites should be considered a premalignant condition for squamous cell carcinoma and should not be treated with conservative therapy.<sup>8</sup> One review found 28 cases of squamous cell carcinoma secondary to HS, all of which affected nonaxillary sites.<sup>8</sup> This highlights the importance of long-term follow-up and early treatment of these patients if indicated. Furthermore, male patients with genitoperineal HS have been found to delay presentation for medical care an average of 5 years more than their female counterparts, often resulting in significant symptom burden at initial evaluation.<sup>9</sup>

Medical and surgical treatment of HS has not been thoroughly characterized in the literature due to the relative rarity of the disease. We aimed to describe the most recent literature relating to genitoperineal HS, particularly new advances in biologic and surgical therapy.

## METHODS

A review of the literature was conducted via PubMed, EMBASE, and Cochrane using keywords of HS, surgical intervention, perineal/genital region, and biologic therapies.

PubMed resulted 150 articles, 113 of which were reviewed after filtering for “English” and “humans.” Randomized control trials (RCTs), case series, and reviews were included without a limit on a date range. Exclusion criteria included articles reporting only 1 case study, commentaries, poster/conference presentations, or series limited to complications of disease without treatment overview. Using these selection criteria, 43 studies and 13 review articles were ultimately thoroughly reviewed. Similar criteria were applied to Cochrane and EMBASE. Cochrane yielded 4 publications, 1 of which was a review of specifically RCTs in HS care, and the remaining 3 were ongoing trial publications. EMBASE returned 243 articles, with 56 as duplicates from the PubMed search. Applying the aforementioned selection criteria to the EMBASE query resulted in 56 articles for thorough review and 16 more review publications.

## RESULTS

There was a paucity of literature on the medical and surgical treatment of genitoperineal HS. RCTs are infrequently used to compare surgical treatment methods for patients with HS. A

review published in 2016 found only 11 studies in the literature meeting their inclusion criteria that used RCTs to evaluate efficacy of various treatment modalities. Only 1 of the RCTs described compared surgical methods.<sup>10</sup>

## DISCUSSION

Treatment of HS has historically followed a generalized progression that usually begins with attempted medical therapy followed by escalation to surgical intervention.<sup>4,11</sup> It is typical for patients to attempt multiple therapies, often prior to any formal diagnosis. Although disease progression and timeline of trialed interventions may vary, many patients experience a protracted course of management with various medical therapies before any coordinated surgical intervention. Medical therapies include antibiotics, acne treatments, topical and systemic steroids, antiandrogen therapy, immunosuppressive agents, and biologic therapy.<sup>4,12</sup> There is a tendency to utilize medical therapy first-line for HS patients until their disease evolves significantly or they become refractory to nonsurgical intervention. However, surgery is more successful at reducing recurrence rates when used in combination with medical therapy than when medical therapy is used alone.<sup>4,13</sup> One study comparing outcomes of oral acitretin 0.5 mg/kg only vs wide excisional surgery plus oral acitretin in patients with HS Stage II found the recurrence rate to be 40% vs 20%, respectively.<sup>13</sup> Ultimately, genitoperineal HS may significantly affect an individual's quality of life and should be considered when making a treatment plan. This, in combination with the often delayed presentation and diagnosis of patients, may appropriately prompt a more aggressive therapeutic management. Although some patients may be hesitant to proceed with wide excision surgery, it is incumbent on us as physicians to educate our patients on the limited utility of topical antibiotics and the necessity of recurrent maintenance therapy if biologics alone are to be used. While our current understanding of HS pathophysiology is not fully elucidated, we should still use the growing body of research demonstrating that early surgical intervention in combination with biologic therapy has the best success in achieving disease remission to inform our practice.

### Nonbiologic Medical Therapy

Topical and oral antibiotics treat secondary bacterial infections in HS and serve as an anti-inflammatory agent but do not modify the disease progression. Treatment of mild HS starts with topical antiseptic solutions or antimicrobials like clindamycin.<sup>11</sup> Step-up therapy from topical treatment often begins with oral tetracycline therapy.<sup>14</sup> One RCT of 46 patients compared use of topical clindamycin 1% solution with oral tetracycline 500 mg twice daily and found no statistical difference in success between the 2 treatments<sup>15</sup>; however, a Cochrane systematic review identified this as low-grade quality of evidence due to the few subjects and high attrition rate.<sup>16</sup>

Some providers utilize combination therapy like oral clindamycin and oral rifampicin when patients are refractory to topical antibiotics or other single therapies.<sup>17</sup> One

review found that among 34 patients with various stages of HS treated with clindamycin or rifampicin, 82.4% and 47% showed treatment response and total remission, respectively.<sup>17</sup> Of those that achieved remission, 61.5% of patients had a relapse within 5 months of stopping treatment. Of note, nonresponders in this series had more severe disease at baseline.<sup>17</sup> Combined therapy with clindamycin and rifampin has not been adequately studied.

It is unknown whether the primary benefit of antibiotic use in HS is derived from an antimicrobial or anti-inflammatory effect.<sup>18</sup> Many studies have demonstrated sterile wound cultures taken from patients with HS, and concluded that positive cultures tend to either be skin contaminants or as a result of secondary infection.<sup>6</sup> Medication choice, dosage, or duration of treatment has not been well studied. Consequently, the choice of whether to use antibiotics for flares, maintenance treatment, or in preparation for surgery remains vague when considering risk of antibiotics, such as resistance, *Clostridium Difficile* infection, and individual side effects.<sup>18</sup> Based on what limited data exists, it can be concluded that antibiotics do not afford cure for HS and may be best used as adjuvant therapy to surgical intervention.

### Biologic Therapy

Ongoing investigation into biologic therapy, specifically antitumor necrosis factor (TNF) agents like etanercept, adalimumab, and infliximab, continue to evaluate success in the treatment of HS. Two recent RCTs, PIONEER I (207 patients) and II (326 patients), investigated the efficacy of adalimumab as monotherapy or in conjunction with antibiotics in patients with moderate to severe HS as compared to placebo.<sup>19</sup> Of participants receiving the intervention of adalimumab in both PIONEER I and II, 41.8% and 58.9%, respectively, reached the primary outcome of a reduction in disease burden by greater than 50%. Dual therapy with antibiotics and baseline Hurley Stage did not significantly affect efficacy.<sup>19</sup> These 2 large RCT's are significant on 2 points: Hurley Stage did not impact efficacy of adalimumab, and combination with antibiotics did not demonstrate synergistic improvement. As antibiotics were described to have limited use in severe HS in the aforementioned section, the significant treatment response of adalimumab in moderate to severe HS is notable.

Smaller RCTs assessing infliximab and etanercept demonstrated a clinical benefit in infliximab but not etanercept. Infliximab resulted in a statistically significant improvement in patients with moderate to severe HS.<sup>20</sup> Another RCT enrolled 20 patients with HS and found no statistical difference in improvement between those patients receiving 50 mg of etanercept twice weekly subcutaneously and those receiving placebo.<sup>21</sup> A number of smaller series showed efficacy of infliximab in achieving remission, although benefit was contingent upon ongoing infusions. A recent study demonstrated that 12 patients treated off-label with infliximab for HS all responded with clinical improvement from baseline and 75% reported a "life-changing response."<sup>22</sup> Lastly, a study concluded that

among 16 cases of HS treated in prior years with infliximab, there was generally remission of disease that then returned upon discontinuation of the drug.<sup>23</sup> The authors concluded that ongoing infusions of infliximab are more likely to keep a patient in remission or prepare him or her for surgery by medically decreasing/improving disease burden.<sup>23</sup> The success rates of achieving remission of HS with use of adalimumab are promising; however, larger RCT's with longer follow-up and use in combination with surgical intervention should be investigated. Currently, adalimumab is the only Food and Drug Administration (FDA)-approved biologic medical treatment for HS.

### Surgical Therapy

Surgical techniques for the treatment of HS have included incision and drainage, deroofing, and varying degrees of excision.<sup>4,24</sup> Incision and drainage is often utilized for acute relief of a fluctuant abscess; however, this has no intrinsic preventative benefit of disease recurrence or progression.<sup>25</sup> One study reported 100% recurrence of disease within 3 months of having an incision and drainage performed.<sup>25</sup>

A retrospective study of 590 consecutive patients with HS Stage III compared the outcomes of patients who underwent incision and drainage, deroofing, and wide excision procedures.<sup>1</sup> They found a total recurrence rate at the site of surgical intervention of 24.4%, which was significantly higher in those who underwent incision and drainage.<sup>1</sup> Early data with surgical excision revealed low recurrence rates for axillary (3%) and perianal surgery (0%) and higher recurrence rates for submammary (50%) and inguinoperineal (37%).<sup>26</sup> More recent studies have



**Figure 2.** Wide local excision. (Color version available online.)



**Figure 3.** Postoperative results. (Color version available online.)

**Table 1.** Genitoperineal hidradenitis suppurativa treatment flow chart

Stage	Treatment Recommendations
Hurley stage I	Multi-disciplinary team evaluation: Medicine/rheumatology, wound care (if necessary) plastic surgery/colorectal surgery (if appropriate)
Hurley stage II	Weight loss, smoking cessation, meticulous hygiene, diabetes control and/or topical antibiotics Stage I measures plus: local and systemic therapies (including immunotherapies), and minor surgical procedures
Hurley stage III and/or recurrent stage I ± II	Stage II measures plus: Wide surgical resection, skin graft, wound care with concurrent systemic therapy

demonstrated that management with local incision vs wide excision (Fig. 2) have recurrence rates of 22.0% and 13.0%, respectively.<sup>27</sup> As wide excision was found to have lower recurrence rates, this technique has become more popularized. In a meta-analysis of recurrence rates after surgical treatments for HS of all body areas, patients treated with wide excision group had recurrence rates of: 15% with primary closure, 8% with flaps, and 6.0% with grafting.<sup>27</sup>

After surgical resection, surgeons use primary closure, split-thickness grafts (STSG), flaps, and healing by secondary intention in order to allow healing.<sup>2,28</sup> Special consideration may be given to surgical method in the case of perineal or genital region due to more delicate tissue/skin covering the penis and scrotum as well as psychosocial and cosmetic considerations (Fig. 3).<sup>29</sup>

With psychosocial and functional aspects of the genitalia, special techniques may be required to fulfill both patient and partner expectations. Chen et al achieved 60%-100% take-of-skin coverage with STSG of penis and scrotum and no wound complications secondary to either STSG or flaps in a cohort of 6 patients.<sup>28</sup> It has been found that unmeshed grafts are preferable for patients who desired postoperative erectile and sexual function.<sup>30</sup> This in part due to anticipated better cosmetic outcomes and increased flexibility.<sup>30</sup> Patients have described “cosmetically acceptable outcomes” with normal ability to void without decreased sexual function from baseline. Flaps, however, may reduce the risk of contractures and unwanted scarring; however, they carry the risk of recurrence depending on the region and extent of disease.<sup>12</sup> Various authors have concluded that risk of recurrence is associated with extent of excision and not the method of wound closure.<sup>31,32</sup> While the ideal closure typically involves a combination of all techniques, the choice of wound closure technique is based on functionality, ease and duration of wound healing, cosmesis, and affected areas of the body as opposed to impact on disease progression.<sup>2,28,33</sup>

Patients with Hurley Stage II or III will often eventually turn to surgical modalities for treatment despite inherent invasiveness given the opportunity for durable cure after long-term suffering. In a survey of over 100 patients with HS who underwent various surgical treatments, 85% expressed extremely high rates of satisfaction with surgical outcomes and 96% were glad they had undergone surgery.<sup>34</sup>

While both medical and surgical treatment of genitoperineal HS have demonstrated efficacy, recent data shows that the combination improves results. The use of antibiotic

regimens perioperatively is standard; however, the newer biologic treatment modalities are less studied in the perioperative period. Concerns have been raised regarding possible delayed wound healing, increased infection and possible graft complications when considering continuing biologic therapy in the perioperative period for combined multimodal therapy. One of the first studies on this topic, Defazio et al retrospectively reviewed the data of 21 patients who underwent treatment for their HS.<sup>35</sup> Eleven of their patients suffered from genitoperineal HS.<sup>35</sup> Patients were treated with surgery alone and compared to patients treated with surgery combined with targeted biologic therapy. They found that patients treated with adjuvant biologic therapy experienced significantly lower rates of recurrence and disease progression.<sup>35</sup> Additionally, no increased complication rates were observed in the biologic therapy group. A few other studies, although with small patient cohorts, have been completed with similar results. At several institutions, including ours, combined biological therapy in conjunction with surgical treatment has demonstrated encouraging outcomes and thus become standard therapy for the appropriately selected patient (Table 1).<sup>36,37</sup>

## CONCLUSION

Although the treatment of HS has typically followed a step-wise approach to using progressively more invasive therapies, management should be tailored to the individual's disease burden and desires. Many studies have concluded that surgical resection of HS should be recommended to patients earlier on in the treatment course in order to provide the best option for remission.<sup>2</sup> Studies have shown that conservative therapies alone may lead to a protracted course and further disease progression such as sinus tract formation and scarring. While surgical excision and reconstruction are currently the guideline driven mainstay of severe genitoperineal HS, early outcomes of multidisciplinary directed multimodal therapy with adjunctive biologic immune modulation in combination with surgery may offer the best longterm outcomes for patients with this disease process. Given the particularly significant psychosocial and functional impact of HS on patients with genitoperineal disease, there is an opportunity to involve a multidisciplinary clinical team earlier allowing for a coordinated medical and surgical care early in the disease process.

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## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.10.013>.

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