Hidradenitis Suppurativa (Acne inversa): Management of a Recalcitrant Disease

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Abstract: Hidradenitis suppurativa is a chronic relapsing disorder of follicular occlusion that is often recalcitrant to therapy. Topical and systemic antibiotics, hormonal therapies, oral retinoids, immunosuppressant agents, and surgical treatment are some of the therapeutic alternatives used for this often recalcitrant and frequently troublesome disorder. This article reviews the pathophysiology of hidradenitis suppurativa, an evidence-based analysis of standard treatments, and recent advances in the therapy of this disorder.

Hidradenitis suppurativa (HS) is a disease of the apocrine gland-bearing areas of the body that commonly affects the intertriginous areas. Although it may initially present in a mild form, recurrent abscesses with the development of sinus tracts and scarring generally ensues. Rather than a distinct disease entity, it may represent the severe end of a spectrum of disease that includes acne. Hidradenitis suppurativa has a prevalence estimate of 1:300 (1). Not surprisingly, HS may have a severe deleterious psychosocial impact on the patient, due to both its chronic nature and lack of response to standard therapeutic options. Side effects of therapy often negatively impact on the patient’s well-being.

PATHOPHYSIOLOGY AND NATURAL HISTORY

The term hidradenitis suppurativa derives from the Greek words hidros for sweat and adne for gland. However, this term may be a misnomer, as it appears that HS may not be a primary disorder of the apocrine glands (2,3), with the inflammation of apocrine glands that occurs likely representing a secondary phenomenon resulting from follicular plugging (3). It is now believed that HS is primarily an inflammatory disorder of the hair follicle and, therefore, is included in the follicular occlusion tetrad along with acne conglobata, dissecting cellulitis, and pilonidal sinuses (4) (Table 1). As well, the “suppurativa” may be inappropriate, as HS is likely not initiated by infection. A more appropriate term may be “acne inversa,” a label preferred by some experts (4,5).

Histopathology of the Disease

In a review in 2005 by Sellheyer and Krah (4), serial histologic specimens show progression from follicular hyperkeratosis and comedo formation to rupture of the follicular infundibulum, with resultant inflammation of the surrounding dermis. Over time, a granulomatous infiltrate is seen, with further local inflammation causing abscess formation and apocrinitis as the inflammation spreads. Of note, early specimens only show the follicular

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occlusion with sparing of the apocrine glands. The authors present a convincing argument for apocrinitis as a secondary effect caused by extension of the inflammatory process.

Clinical Presentation

Clinically, HS usually presents as tender subcutaneous nodules in the intertriginous areas, which include the axillae, inguinal, anogenital, and mammary areas. It has been noted in association with Crohn disease (6,7), Dowling-Degos disease (8–10), and arthropathy (11,12). Although the exact pathophysiologic mechanisms are still unknown, genetics (13–15), hormones (16–18), obesity (18), bacterial infection (19), and smoking (20) may play a role. With time, the follicular occlusion leads to dilatation and rupture of the structure, which sets off a chain of events including inflammation, abscess formation and, in established disease, sinus tract formation, which are classically resistant to treatment. Squamous cell carcinoma is a rare complication of chronic, severe, hidradenitis suppurativa (21–23).

STAGING OF HIDRADENITIS SUPPURATIVA

Mild HS is usually noted early in the course of the disease, and consists of solitary nodules with minimal pain and no abscess formation (Fig. 1). Moderate HS can be classified as multiple recurrent nodules affecting the patient’s daily activities due to pain, discharge or drainage. Abscess formation occurs at this stage (Fig. 2). Severe HS develops late in the course of the disease and involves diffuse abscess formation with chronic draining sinus tracts. Chronic inflammation is evident in multiple areas of scarring (Fig. 3). Fortunately, not all patients progress to severe disease.

MEDICAL TREATMENT

General

First line therapy consists of conservative management, which is subsequently often used in conjunction with other treatment modalities. Initial measures include cessation of smoking, weight loss, and avoidance of irritation in the affected area. Patients should wear loose-fitting cotton clothing and avoid heat, humidity, shaving, depilation, and deodorants. Warm compresses and topical antiseptic or antibacterial soaps can be used for inflamed lesions. Although no controlled trials of these general measures have occurred, the consensus among practitioners is that general preventative measures can help with the symptoms of mild HS.

Antibiotics

Conservative measures may not be enough to control the disease and systemic and/or topical antibiotics can be added to the treatment regime. Topical clindamycin (24) is a good choice for initial therapy. A double-blind
placebo controlled study showed that topical clindamycin for 3 months resulted in significant improvement, and a recent double-blind trial showed that topical clindamycin was just as efficacious as systemic tetracycline. However, concern regarding the emergence of resistant bacteria following prolonged therapy is a reasonable factor impacting on treatment plans.

Of the systemic antibiotics, tetracycline, minocycline, and erythromycin are among those commonly used for chronic treatment of HS. Most information comes from anecdotal evidence and case reports. However, a recent small retrospective study showed remission of HS using a 10-week course of combination 300 mg of clindamycin twice daily and 300 mg of rifampicin twice daily. In this study, the major side-effect was diarrhea, which necessitated discontinuation of the medication in four patients. The remaining 10 patients were maintained in remission up until the time of the report, for a symptom-free duration of 1 to 4 years.

**Hormonal**

Although most patients with HS have normal androgen profiles, improvement of HS with the use of antiandrogens has been reported. The mechanism may be due to altered end-organ sensitivity to androgens. The two agents best studied are cyproterone acetate and finasteride. In a study, using 50 µg of ethinyloestradiol/50 mg of cyproterone acetate daily, 50% of the women showed improvement, with approximately 30% having complete remission for 18 months. Another report demonstrated clinical control using 100 mg/day of cyproterone acetate in four women with long-standing HS; unfortunately this drug is not available in the US due to its potential hepatotoxicity and theoretical concerns regarding feminization of male fetuses. Data are lacking on the use of other oral contraceptives in HS, and the rationale for their use is largely based on anecdotal reports and clinical data confirming that oral contraceptives are useful in the treatment of acne.

Recently, a few case series demonstrated clinical improvement in both male and female HS patients following the use of finasteride, a selective inhibitor of type-II 5-a-reductase. However, finasteride is associated with a number of side-effects, including teratogenicity, decreased libido, erectile dysfunction, decreased ejaculatory volume, gynecomastia, and breast enlargement in women. Nonetheless, because of its rapid and almost complete elimination, some have suggested that it may be safer than retinoids for women of childbearing age.

**Oral Retinoids**

Isotretinoin is a useful medication in the treatment of acne and has been used in HS as well. However, despite earlier reports of success with isotretinoin, a recent retrospective study of 68 patients showed that less than a quarter (23.5%) had clearing with a 4–6 month course of low-dose isotretinoin and only 16.2% showed maintenance of improvement on follow-up. In this study, the mean daily dose was 0.56 mg/kg/day. No large studies with standard doses of isotretinoin have been performed. However, success with acitretin and etretinate, including in patients who have failed courses of isotretinoin, has been reported.

**Dapsone**

Dapsone has been found to be helpful in a small number of HS patients and is a reasonable therapeutic alternative for recalcitrant disease. In a recent series of five patients, clinical improvement was noted in all five within 4 to 12 weeks, utilizing doses between 25 and 150 mg daily. No significant adverse effects were noted. As with all patients on dapsone, it is important to monitor the hemoglobin levels and to screen for glucose-6-phosphatase deficiency.
Immunosuppressive Therapy

Systemic and intralesional corticosteroids may be used for their nonspecific anti-inflammatory effects. Systemic steroids carry with them a higher risk of side effects including hypertension, cushingoid features, and adrenal axis suppression. Although initial control may occur, many patients will flare as steroid therapy is tapered or discontinued. Intralesional steroids are of benefit to patients in the short term, although evidence is lacking to support this as a long-term form of disease control. A total of four patients have been reported, documenting improvement with cyclosporin (45–47). One must keep in mind the risk–benefit ratio when using this drug, and long-term use is probably not warranted in most instances, given the risks of hypertension and renal impairment that increase with prolonged treatment.

Biologics

Considerable interest exists in the possible benefits of biologic agents for HS. The most experience has accrued with infliximab, a chimeric monoclonal antibody with high affinity for tumor necrosis factor-alpha. The initial report involved a patient with Crohn disease and axillary HS who received infliximab for her Crohn disease (48). The HS showed significant improvement after one dose and cleared completely after the second dose. Subsequently, nine patients with HS who responded to infliximab have been reported (49–53). Success with etanercept and adalimumab has also been described (54,55). However, treatment with any of these agents carries significant risks. Side effects include infusion reactions, serum-sickness reaction, reactivation of latent tuberculosis (TB), immunosuppression, exacerbation of demyelinating diseases, lupus-like reactions, and the potential development of late lymphomas (56–58). A fatal occurrence of epidermoid carcinoma has been reported following treatment with infliximab (59). Although the use of biologics is promising, the decision must be made with serious consideration for the potential severe side effects.

Other Medical Treatments

Other modalities that have been used for HS include radiotherapy (60), ALA-PDT (61,62), botulinum toxin A (63), granulocyte–macrophage colony-stimulating factor (GM-CSF) (64), cryotherapy (65), and methotrexate (66). Unfortunately the data supporting the use of these agents consist of isolated case reports with attendant selection bias.

SURGICAL TREATMENT

Although medical treatments are often used in early stages of HS, once scarring develops, surgical interventions become the preferred mode of treatment. The goal in surgery is to remove the scarred tracts and draining abscesses. Although the best mode of surgical therapy has yet to be determined, consensus has been reached regarding several general principles. First, incision and drainage of an inflammatory lesion is of limited value and should be avoided (19,67). However, marsupialization of recurrent lesions may aid with local control (68). Second, the surgical literature suggests that surgical removal of the involved tissue is the treatment of choice (69–71). However, depending on the extent of disease involvement, this may not be feasible. Unfortunately recurrences happen even following wide surgical excision. A recent study showed 100% recurrence after drainage, 42.8% after limited, and 27% after radical excision (67). As well, a series of 82 patients with 118 radical excisions showed high recurrence rates for...
inguinoperineal and submammary disease (72). A large study of 106 patients and 143 excisions showed a recurrence rate of almost 70% following primary closure in patients with mild to severe HS (73). However, all varieties of flaps and grafts have been used for more extensive disease with no major recurrences (70).

Various modalities of surgery have been used, from the traditional scalpel to the use of CO₂ laser (74–78). While surgical excision is definitely a treatment option for chronic and intractable disease, it carries the risk of additional scarring. Although curative surgery is possible, the chance of recurrence is a real and potential outcome. Other complications include contractures and functional loss or limitation of mobility, secondary to fibrosis and scarring (79).

**STEPWISE APPROACH TO MANAGEMENT OF HS**

In light of our current understanding of this disease, and the quality of evidence in support of the various therapies available, a stepwise approach to management has been designed (Table 2). Unfortunately, no level-1 high-quality data from appropriately designed trials of significant size are available, and recommendations are therefore limited by this shortcoming.

For the purposes of examining the levels of evidence, three methods for evaluating and grading were considered. The first method was that of the Oxford Centre for Evidence-based Medicine Levels of Evidence (http://www.cebm.net/levels_of_evidence.asp). We found this method quite extensive and comprehensive. The advantages were the strict definitions of each category and the inclusion of grades of recommendation. However, this method has drawbacks. The level of complexity makes the system difficult to access for the practitioner (i.e., level-1 evidence is split into a, b, or c depending on further qualifications to the evidence). As well, there is no weight placed on clinically relevant outcome versus purely numerical outcomes (i.e., reduction in deaths versus lowering of cholesterol numbers). For this reason, an attempt was made to identify another method of evaluation. A second method considered was that of the US Preventive Services Task Force (USPSTF).

### TABLE 3. Levels of Evidence for Select Medications in the Treatment of HS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Quality of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1% solution</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Systemic antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin/Rifampin</td>
<td>Clindamycin 300 bid</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Other antibiotics</td>
<td>Variable</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyproterone</td>
<td>100 mg/d</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Other oral contraceptives</td>
<td>Variable</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Finasteride</td>
<td>5 mg/day</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Oral retinoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Variable (low dose, 0.7–1.2 mg/kg/day)</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Variable</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (intralesional)</td>
<td>Variable</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>2–4.5 mg/kg/day</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Biologics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 mg/kg repeated at 2 wks and 6 wks</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg s.c. twice weekly</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg s.c. every other week</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Other (medical)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>25–150 mg/day</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>ALA-PDT</td>
<td>N/A</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>MTX</td>
<td>12.5–15 mg weekly</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>N/A</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Botox</td>
<td>250 U Dysport as for hyperhidrosis</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>450 µg in 10 mL of 0.9% NaCl solution</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>N/A</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Surgical therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local excision</td>
<td>N/A</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Radical excision</td>
<td>N/A</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>CO laser</td>
<td>N/A</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

HS, hidradenitis suppurativa; GM-CSF, granulocyte–macrophage colony-stimulating factor.
Although this is also an excellent system to stratify quality of evidence and contains categories of recommendations, it did not distinguish between numerical and clinically relevant outcomes. In addition, the system is designed for populations and for public health professionals, and not for individual studies.

For these reasons, we elected to use the system proposed by Ebell et al (80) (Appendix 1) which includes the benefits of an easy-to-use system with clinical and patient-oriented recommendations. The findings of our analysis of the data on treatments for HS are summarized in Table 3.

**TABLE 4. Side-Effect Profile of Select Medications in the Treatment of HS**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side-effect profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin and rifampin</td>
<td>Discoloration of body fluids (rifampin), pseudomembranous colitis (clindamycin), selection of resistant organisms, vulvovaginal candidiasis</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Teratogenicity, decreased libido, erectile dysfunction and gynecomastia (males), breast enlargement (females)</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Mood lability, pseudotumor cerebri, hypertriglyceridemia, pancreatitis, hepatic transaminitis, myalgias, xerosis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Serum sickness reaction, reactivation of latent tuberculosis, immunosuppression, exacerbation of demyelinating diseases, lupus-like reactions, latent lymphoma (potential)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Hemolytic anemia, methemoglobinemia, blood dyscrasias, hepatitis, peripheral neuropathy, lupus-like reaction, mood lability, erythema multiforme</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Local pain, scarring, prolonged healing time, posttreatment infection</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Myelosuppression, hepatotoxicity, nausea, nephropathy, interstitial pneumonitis</td>
</tr>
<tr>
<td>Botulinum toxin A</td>
<td>Pain at injection site</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Hypertension, pancreatitis, blood dyscrasias, immunosuppression, hepatotoxicity, hypomagnesemia, hirsutism, gingival hyperplasia, hypertrichosis, nephrotoxicity</td>
</tr>
<tr>
<td>ALA-PDT</td>
<td>Local pain and irritation</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Transaminitis, fluid retention, venous thrombosis, ‘first dose’ reaction (fever, hypotension, tachycardia, rigors, flushing, nausea, vomiting, dyspepsia)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Carcinogenic risk, myelosuppression</td>
</tr>
</tbody>
</table>

HS, hidradenitis suppurativa; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Although this is also an excellent system to stratify quality of evidence and contains categories of recommendations, it did not distinguish between numerical and clinically relevant outcomes. In addition, the system is designed for populations and for public health professionals, and not for individual studies.

For these reasons, we elected to use the system proposed by Ebell et al (80) (Appendix 1) which includes the benefits of an easy-to-use system with clinical and patient-oriented recommendations. The findings of our analysis of the data on treatments for HS are summarized in Table 3.

**CONCLUSION**

Hidradenitis suppurativa is a complex and recurrent disease that can be socially and medically debilitating. Although initially thought to be a disease of the apocrine glands, it is now clear that the primary pathogenic event is follicular occlusion, with subsequent inflammation. A number of treatment options are available for HS, including general measures, topical and systemic antibiotics, hormonal treatments, systemic retinoids, local and systemic immunosuppressants, as well as biologic agents. The benefits of these therapies must be weighed against their side effects (Table 4). It must also be kept in mind that the disease is characterized by recurrences regardless of medical treatment modality used. Surgical treatment is another therapeutic option, particularly in later-stage disease characterized by sinus tract and fistula formation. Large, randomized, controlled studies would be helpful in identifying best treatment options, as no level-1 data currently exist regarding the optimal treatment for this debilitating and frequently frustrating disease.

**REFERENCES**


APPENDIX 1: REFERENCES FOR QUALITY OF EVIDENCE AND GRADING OF RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Study quality</th>
<th>Level 1</th>
<th>Definition (for treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR/meta-analysis of lower quality clinical trials or of studies with inconsistent findings</td>
<td>High-quality individual RCT*</td>
<td></td>
</tr>
<tr>
<td>Case-control study</td>
<td>All-or-none study*</td>
<td></td>
</tr>
<tr>
<td>Cohort study</td>
<td>Level 2</td>
<td></td>
</tr>
<tr>
<td>Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series for studies of diagnosis, treatment, prevention, or screening</td>
<td>Level 3</td>
<td></td>
</tr>
</tbody>
</table>

Strength of recommendation taxonomy (SORT)

<table>
<thead>
<tr>
<th>Strength of recommendation A</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation based on consistent and good quality patient-oriented evidence†</td>
<td></td>
</tr>
</tbody>
</table>
Recommendation based on inconsistent or limited quality patient-oriented evidence

Recommendation based on consensus, usual practice, disease-oriented evidence or case series for studies of diagnosis, treatment, prevention or screening

Adapted from Ebell et al (80)

*High-quality RCT: allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (>80%).

†In an all-or-none study, the treatment causes a dramatic change in outcomes, such as antibiotics for meningitis or surgery for appendicitis, which precludes study in a controlled trial.

‡Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).

Consistent: Most studies found similar or at least coherent conclusions (coherence means that differences are explainable) or if high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation.

Inconsistent: Considerable variation among study findings and lack of coherence or if high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation.