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Hidradenitis Suppurativa: A Guide for the Practicing Physician

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Abstract

Hidradenitis suppurativa is a chronic inflammatory disease of apocrine gland–bearing skin. Although immunologic derangements, genetic predisposition, obesity, and smoking are likely important factors, the pathogenesis of the disease and the effect of available treatments on disease course have not been fully elucidated. In the absence of proper treatment, chronic inflammation results in diffuse scarring and a wide array of complications, including the development of cutaneous squamous cell carcinoma. This severe and chronic disease can have detrimental effects on self-esteem and quality of life. No ideal treatment regimen has been defined, but several therapies have been found to reduce lesion severity and improve symptoms. We reviewed the literature through July 2014 for existing treatments. Published articles were obtained via systematic review of medical databases (PubMed, Embase, Google Scholar) and scrutiny of citation lists using the search terms "hidradenitis suppurativa" and "acne inversa". Given the scarce literature on treatment strategies, we also reviewed data from any case reports or prospective and retrospective studies that were located. On the basis of the existing literature, we provide an evidence-based algorithm for the management of this disease in the primary care setting. More research is needed to evaluate the comparative effectiveness of topical and systemic treatments and to better understand the pathogenesis, natural history, and subtypes of hidradenitis suppurativa.

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Hidradenitis suppurativa (HS) is an inflammatory disease of apocrine gland–bearing skin with a chronic intermittent course and a devastating effect on quality of life. It is characterized by tender, deep-seated inflammatory nodules and abscesses, sinus tracts, and extensive scarring.[1,2]

Although the effect of current therapies on the course of HS has not been defined, early diagnosis and aggressive control of disease is important in theory, because the destruction of cutaneous architecture that accompanies advanced disease is extremely challenging to treat and associated with debilitating medical and psychosocial sequelae. Estimated reported delays from disease onset to diagnosis range from 7 to 12 years, suggesting that increasing physician and patient awareness of HS remains an important goal.[3,4] Hidradenitis suppurativa is commonly encountered in the primary care setting and may be increasing in incidence.[5] It is managed by general practitioners, dermatologists, and various surgical specialties—a fact that underscores the importance of widespread physician familiarity with its presentation and management.

At present, there are few double blinded randomized trials and no official algorithm to inform the treatment of HS. This leads to heterogeneity in treatment practices because physicians are left to dissect a large and complex literature on their own. Herein, we review the literature pertaining to the clinical features, pathogenesis, and treatment of HS and provide an evidence-based algorithm for its management in the primary care setting.

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PREVALENCE AND NATURAL HISTORY

The point prevalence of HS has been estimated to be between 0.1% and 4.1%. Both familial and sporadic cases have been described. Although cases have been reported in children (most often in the context of precocious adrenarche), the disease most often appears after puberty—commonly in the second and third decades of life—and is rare in the elderly.[6] Several studies have confirmed a strong female preponderance.[5] A racial predilection has not been firmly established.[7]

The course of HS is prolonged and marked by intermittent periods of activity and remission.

ARTICLE HIGHLIGHTS

- Important lifestyle modifications include smoking cessation, weight loss, and avoidance of tight-fitting clothing.
- Comprehensive treatment should include optimization of associated comorbidities and management of pain and psychological sequelae.
- Evidence supports the use of medical therapies including topical and oral antibiotics, oral contraceptives, acitretin, cyclosporine, dapsone, and tumor necrosis factor inhibitors.
- Combining medical therapy with early surgical management (deroofing, local or radical wide excision, and laser ablation) may yield better outcomes.
- We recommend a maintenance regimen of topical clindamycin and cleansing agents such as chlorhexidine gluconate solution 4.0% or benzoyl peroxide for all patients.

Lesions may rupture spontaneously, developing into intradermal or subcutaneous epithelial-lined sinus tracts.[4] In the absence of proper treatment, normal skin is compromised by persistent draining sinuses and the severe dermal scarring that ensues.[4]

Long-standing, poorly controlled disease can lead to a wide array of complications. Diffuse fibrosis and scarring, especially with axillary disease, can lead to limb contractures and impaired mobility. Complications of chronic suppuration include anemia, hypoalbuminemia, and amyloidosis; the last 2 rarely progress to renal failure.[8,9] Other complications include axial and peripheral arthropathy, peripheral lymphedema, fistula formation, and the development of squamous cell carcinoma in areas of chronic inflammation; the last complication has been estimated to occur at a 4.6-fold increased rate compared with unaffected populations.[7,10-12] Psychosocial sequelae of HS include decreased quality of life and work productivity, sexual disturbances, depression, and social isolation.[13-19]

CLINICAL FEATURES

The diagnosis of HS is made on a clinical basis via recognition of the typical morphology (Figure 1), typography, and course of the disease.

Predilection sites, in order of decreasing frequency, include axillary, inguinal, perianal and perineal, mammary and inframammary, buttock, pubic region, chest, scalp, retroauricular, and eyelid.[20]

Clinical severity is graded using the Hurley staging system[21] (Table 1) and Sartorius scoring system.[22] Risk factors for greater disease severity have been investigated in a handful of studies and include male sex; disease duration; body mass index (calculated as the weight in kilograms divided by the height in meters squared); smoking-pack years; presence of axillary, perianal, or mammary lesions; personal history of acne; spontaneous/nonfamilial HS; and involvement of atypical locations (eg, ears).[23,24]

Although chronicity and recurrences are hallmarks of HS, there is substantial variability in its course. This complicates both the diagnosis of HS and its treatment, because heterogeneity in response to treatment (eg, disease activity) may presumably be the result of undetected clinical subtypes differentially responding to different treatment modalities. Three clinical subtypes of HS have been recently proposed using latent class analysis in a large prospective cross-sectional study (N=618): (1) a classic axillary-mammary HS subtype, representing 48% of cases and characterized by breast and axillary involvement and hypertrophic scarring; and 2 "atypical" subtypes: (2) a follicular HS subtype, representing 26% of cases who were predominantly male smokers with a family history of HS and characterized by follicular lesions, including epidermal cysts, pilonidal sinus, comedones, and severe acne; and (3) a gluteal HS subtype, representing 26% of cases, typically smokers with a lower body mass index, and with morphology characterized by follicular papules, folliculitis, and gluteal involvement.[25] These subtypes have yet to be associated with distinct pathogenic mechanisms or differential responses to therapy, and the extent of overlap between them in a clinical population has not been quantified. It is notable that the authors report an earlier onset, more prolonged, and more severe course for patients with the follicular HS subtype and a more prolonged but less severe course for patients with the gluteal subtype.[25]

METHODS

We searched PubMed, Embase, and Google Scholar, and scrutinized citation lists for reports of treatments used for HS. Given the scarcity of randomized controlled trials (RCTs) for HS (and overall scarcity of treatment data), we also reviewed data from any case reports or

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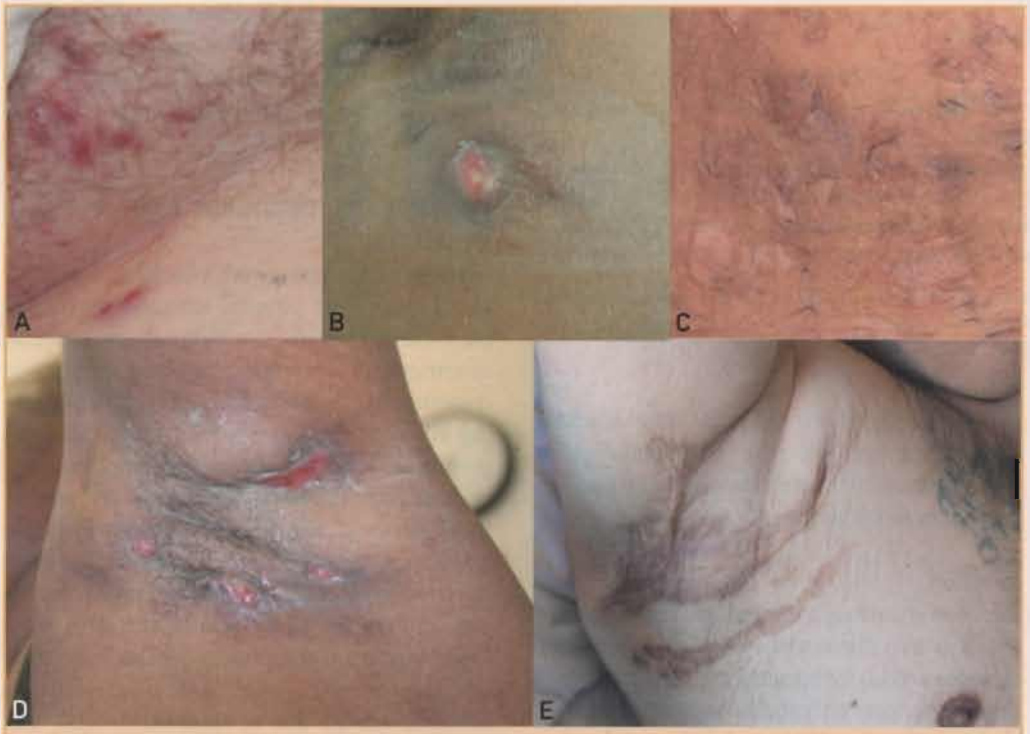

FIGURE 1. Morphology of hidradenitis suppurativa. Typical morphological features include inflamed nodules, abscesses, sinus tracts, and hypertrophic fibrous ("bridged") scarring. Adjacent pairs of comedones ("tombstone comedones") are characteristic of more chronic disease. A, Multiple tender erythematous nodules. B, Abscess. C, "Tombstone" double comedones. D, Draining sinus tracts. E, Bridged, hypertrophic scarring.

prospective and retrospective studies that were located. Search terms included *hidradenitis suppurativa* and *acne inversa*. Only articles in English, published before July 2014, were included. Two authors (A.M.C. and C.M.W.) independently extracted data from relevant articles.

CAUSES AND MECHANISMS OF DISEASE

The pathogenesis of HS has not been fully elucidated and is likely multifactorial. Histopathological studies suggest that hyperkeratosis of the follicular epithelium may be the primary event. Hidradenitis suppurativa likely results from the synergistic effect of the various factors discussed below.

Genetic Factors

A total of 35% to 40% of patients report a family history of HS.[23,24,26] Mutations in the γ-secretase-Notch signaling pathway, which is thought to be involved in epithelial proliferation and differentiation, have been identified in both familial and spontaneous cases, but are overall thought to play an etiologic role in only a minority of cases of HS.[27-30]

Immunological Factors

Elevated levels of several proinflammatory cytokines, most notably tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-17, as well as anti-inflammatory cytokines such as IL-10 have been identified in lesional skin.[31-35] Over- and underexpression of antimicrobial peptides and abnormalities in Toll-like receptor signaling have also been implicated in the pathogenesis of HS, although it is unclear whether these alterations are a primary triggering event or a secondary consequence of bacterial carriage.[32,36,37] One theory posits that the initiating event may be an aberrant immune response to commensal microbes, leading to the production of antimicrobial peptides and cytokines and recruitment of an inflammatory infiltrate. This inflammation, in turn, results in

TABLE 1. Hurley Staging System

Hurley stage	Clinical features
Mild (grade I)	Abscesses only (single or multiple) without sinus tracts or cicatrization
Moderate (grade II)	Abscesses (single or multiple) with sinus tracts or cicatrization. Lesions are distinct and widely separated (eg, >10 cm apart)
Severe (grade III)	Multiple interconnected sinus tracts or abscesses or disease with nearly diffuse to diffuse coverage of an area (eg, axilla)

Patients should be classified according to the Hurley staging system into those with mild (grade I), moderate (grade II), and severe (grade III) disease.
Adapted from *Dermatologic Surgery*,[21] with permission.

hyperkeratosis of the follicular infundibulum, and subsequent follicular plugging, rupture, and activation of the inflammasome by free keratin fibers in the dermis.[38]

Infection

Infection is unlikely to be a primary causative factor. It is hypothesized that follicular occlusion serves as a nidus for bacterial colonization, which may then trigger an immunological response, or alternatively, that HS may be the result of an aberrant response to commensal bacteria.[39]

Smoking

Several studies point to higher-than-average smoking rates (70%-90%) among patients with HS and more severe disease in smokers, but it is unclear whether this relationship is causal.[6,26,40,41] Nicotine may lead to follicular plugging via its promotion of hyperplasia of the follicular infundibulum and oversecretion of eccrine glands or contribute to inflammation by inducing chemotaxis of neutrophils.[42-45]

Obesity

The severity and course of HS are correlated with body mass index.[26,41] Although obesity is known to affect cutaneous physiology in various ways, in the case of HS it is primarily thought to compound the severity of disease through mechanical effects, for example, sweat retention, maceration, and enhanced mechanical friction, and possibly also through coexisting hormonal alterations.[41,46,47]

Androgens

The premenstrual onset and female predominance of HS, along with noted improvements during pregnancy or with antihormonal therapy, suggest that androgens may play a role in the pathogenesis of HS.[48] However, these effects are likely subtle or part of a multifactorial etiology, given that studies have failed to consistently find higher rates of androgenism in HS cohorts as compared with controls.[49,50]

DIFFERENTIAL DIAGNOSIS AND EVALUATION

Features of the history (chronicity and postpubertal onset) and physical examination (multiple inflamed lesions, symmetrical involvement, intertriginous predominance, and tombstone comedones) are usually adequate for distinguishing HS from various other conditions that can present with a similar clinical morphology (eg, nodular acne, developmental fistula, and epidermoid, dermoid, pilonidal, or bartholin cysts). In addition, HS can be distinguished from various infectious entities (eg, abscess, carbuncles, furuncles, actinomycosis, cat scratch disease, granuloma inguinale, lymphogranuloma venereum, nodulоulcerative syphilis, and tuberculous abscess) via the use of bacterial, fungal, and mycobacterial cultures because conventional cultures in HS are typically sterile or grow multiple species as opposed to a single infectious agent.[51,52]

Furthermore, patients with HS are typically afebrile, are clinically well, and have laboratory parameters within normal limits, although patients with more severe disease may have leukocytosis or elevation in their erythrocyte sedimentation rate and C-reactive protein level. Cutaneous manifestations of inflammatory bowel disease, and in particular Crohn disease, should be considered in the setting of perianal lesions and concomitant gastrointestinal symptoms.[53]

Alikhan et al[54] proposed a diagnostic algorithm in which fulfillment of 4 criteria is sufficient for a clinical diagnosis of HS: (1) Is there more than a single inflamed lesion? (2) Is the course chronic with new and recurrent lesions? (3) Are the lesions bilateral? and (4) Are the lesions located primarily in the milk line?

LIFESTYLE MODIFICATION

Weight Loss

A retrospective survey study of patients with HS who had undergone bariatric surgery found that a 15% or greater reduction in weight was associated with a 35% decrease

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in HS symptoms and a significant reduction in the number of involved sites (P=.003).[55] Isolated case reports attest to sustained HS remission after extreme weight loss or bariatric surgery.[56] Despite the lack of a strong evidence base, given the other many benefits of weight loss, we strongly encourage clinicians to counsel overweight or obese patients about the role of obesity in the pathogenesis of HS as well as the possible effect of weight loss on the course of their disease.

Smoking Cessation

The effect of smoking cessation on the course of HS has not been systematically assessed. Supporting evidence is drawn from anecdotal reports, correlational studies, and evidence suggesting that nicotine may play a role in the pathogenesis of HS.[57] Despite the lack of data to substantiate the efficacy of this intervention, we argue that the possibility of clinical improvement, combined with the numerous established benefits of smoking cessation to overall health, is sufficient justification to make smoking cessation a priority in HS management.

Clothing

In theory, avoidance of tight-fitting, restrictive clothing would be beneficial, given the presumed role of friction in the pathogenesis of HS. There are no studies to substantiate this claim, but this intervention can be recommended, given the facility and low risk of implementation.

MEDICAL MANAGEMENT

Antibiotics

Antibiotics are a mainstay of HS treatment, likely because of their both antibacterial and immunomodulatory properties, although evidence for their efficacy is limited. Two blinded RCTs suggest that topical clindamycin 1% twice daily may be an adequate treatment for mild disease, an adjunctive therapy, or a tool to decrease inflammation before radical surgery in more severe disease.[58,59] Overall, systemic antibiotics appear to be effective for a large proportion of patients with mild to moderate but not severe HS: in a retrospective review, improvement in lesions was noted in 79.6% and complete clearance in 26.5% of patients who had received various systemic antibiotic regimens.[60,61] Although monotherapy with doxycycline, amoxicillin with clavulanic acid, clindamycin, other tetracyclines, and ciprofloxacin is common in the clinical setting, only combination regimens have been systematically evaluated.[52] Combination therapy with rifampicin and clindamycin is the most well studied regimen. Partial response rates (some improvement) ranging from 71% to 93% have been reported for 10-week courses of rifampicin 600 mg once daily and clindamycin 300 mg twice daily.[62-65] A total of 11% to 47% of these patients experienced complete remission.[63,65] A maximum therapeutic response is typically obtained within 2.5 months (with no therapeutic benefit with extension), and the mean time to relapse is 5 months.[65] Adverse effects are reported in 13% to 43% of patients, the most common being diarrhea.[62-65] An alternative regimen with broad-spectrum coverage including anaerobes exhibited marginally superior efficacy but lower tolerability: in this retrospective study, combination therapy with rifampin 10 mg/kg once daily, moxifloxacin 400 mg once daily, and metronidazole 500 mg thrice daily (6 weeks only) was administered for up to 6 weeks after complete remission was achieved, followed by secondary prophylaxis with trimethoprim-sulfamethoxazole 400 mg/80 mg once daily or doxycycline 100 mg once daily. Complete remission was achieved in 57% of patients, and a partial response was documented for the remainder. The mean time to remission was 2.4 months for patients with Hurley stage I disease and 3.8 months for patients with Hurley stage II disease. The administration of secondary prophylaxis did not prevent relapse in 58% of patients who achieved remission. Adverse events were common, including nausea and diarrhea (64%), vaginal candidiasis (35% of female patients), and tendinitis (14%).[61] In a recent prospective study, the most common species were coagulase-negative staphylococci, followed by *Staphylococcus aureus* and various strains of intestinal flora, including *Escherichia coli*, *Klebsiella* sp, *Proteus mirabilis*, *Enterococcus faecalis*, and *Pantoea agglomerans*.[52] Sensitivity studies revealed that these species were resistant to most antibiotics commonly used in the clinical setting, including tetracyclines (64%), macrolides (58%), trimethoprim-sulfamethoxazole (54%), lincosamides (51%), and monobactams (75%).[52]

The authors recommend an initial regimen of interchangeable use of amoxicillin with clavulanic acid and fluoroquinolones, followed by clindamycin-rifampicin combination and finally rifampin-moxifloxacin-metronidazole. They also recommend tetracyclines or macrolides for maintenance therapy.[52]

Antiandrogens

In a retrospective comparison, antiandrogen therapy was found to be superior to antibiotic therapy for HS treatment.[66] Overall, a substantial but mostly anecdotal literature points to an important role of antiandrogenic therapy in the treatment of mild to moderate HS. This is in part due to higher rates of polycystic ovarian syndrome (PCOS) in this patient population; as such, concomitant acne, hirsutism, androgenetic alopecia, or a history of irregular menses in a patient with HS should prompt measurement of free and total testosterone, luteinizing hormone, follicle-stimulating hormone, and dehydroepiandrosterone sulfate levels. Interestingly, evidence suggests that antiandrogens may be effective as an adjunctive or monotherapy for HS even in the absence of clinical or biochemical evidence of hyperandrogenism.[67]

Optimal antiandrogen regimens for HS have not been defined. Treatment with a combined oral contraceptive may be especially advantageous for female patients of childbearing age who also require some form of birth control. No difference between ethinyloestradiol 50 μg/norgestrel 500 μg and ethinyloestradiol 50 μg/cyproterone acetate (CPA) 50 mg was found in a double-blind crossover trial in which half of the patients (N=24) exhibited clearance of or improvement in HS over a 12-month period.[68] Combined oral contraceptive with third-generation progestins (including gestodene, norgestimate, and desogestrel), which are less androgenic because they bind more selectively to the progesterone receptor, should be used. Combined oral contraceptive with drospirenone, a synthetic progestin that is an analog of the antiandrogen spironolactone, may be particularly beneficial. Given the high prevalence of smoking in this patient population, combined oral contraceptive, and especially drospirenone, should be prescribed with care because of the increased risk of thromboembolism.[69]

Finasteride, a 5-α-reductase inhibitor that halts the conversion of testosterone to the more active 5-α-dihydrotestosterone, has exhibited beneficial effects in short courses (6-16 weeks) and as maintenance therapy in both female and male patients of varying ages.[67,70,71] In these studies, doses ranging from 5 to 15 mg once daily were administered, which is notably much higher than the doses commonly used for the treatment of benign prostatic hyperplasia and androgenetic alopecia. Even so, these doses were well tolerated and the most common adverse effects were gynecomastia and breast tenderness.[67,70,71] Women of childbearing age should use contraceptives, given the risk of feminization of male fetus. Cyproterone acetate and spironolactone exert antiandrogenic effects via binding to testosterone receptors and inhibition of androgen biosynthesis. Efficacy of CPA for HS has been reported in a few studies, but it is not approved for use in the United States. At present, no data support the use of spironolactone specifically for HS; however, given its equivalence to CPA for the treatment of other conditions associated with hyperandrogenism, such as hirsutism, it may be a viable alternative.[72]

Studies suggest that rates of metabolic syndrome may be disproportionately high in the mostly obese HS population.[73,74] Insulin resistance is also a central pathogenic feature in PCOS because hyperinsulinemia affects ovarian androgen production.[75] Metformin, a biguanide insulin-sensitizing agent, is a first-line treatment of PCOS and type 2 diabetes; a few case reports and a prospective study suggest that it may also be effective in subsets of patients with HS.[76] In a prospective study (N=25) in which metformin was up-titrated to doses of 1.5 mg once daily, clinical improvement was noted in 72% (n=18) of patients, 7 of whom had a more than 50% reduction in Sartorius scores by 12 weeks.[76]

Retinoids

Despite clinical similarities between HS and acne vulgaris, isotretinoin has not been proved to be efficacious in the treatment of HS, even for patients with a history of acne.[77] A systematic review of 7 studies reports an overall nonresponse rate of 64% for isotretinoin administered in daily doses of 0.5 to 1.2 mg/kg for 4 to 12 months.[78] In contrast, evidence suggests that acitretin

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(a metabolite of etretinate with a shorter elimination half-life) may be an efficacious alternative. Reported dosing regimens for acitretin range from daily doses of 0.25 to 0.88 mg/kg and for etretinate from 0.35 to 1.1 mg/kg for 3 to 39 months. In a retrospective study of patients with severe HS (N=12; 8 male patients), all patients were noted to exhibit some improvement, with most of them achieving marked or complete remission on dosing regimens of 0.25 to 0.88 mg/kg for acitretin monotherapy for 5 to 12 months. This is consistent with a response rate of 95% reported in a systematic review that also incorporated evidence from several case reports.[78] Improvement was generally observed by 2 months and continued for the first 6 months of therapy.[79] Long-lasting improvement, with remission periods ranging from 6 to 45 months, was reported for 9 of these patients.[79] Given their teratogenicity, retinoids should be avoided in women of childbearing age. If administered, adequate contraception must be used for the duration of treatment and for the recommended period after drug cessation, which is retinoid dependent.

Zinc Gluconate

One prospective study reported favorable results for monotherapy with zinc gluconate 90 mg once daily for patients with mild to moderate HS: 36% experienced complete remission and the remaining 63.6% partial remission.[80] Doses were decreased as tolerated after a clinical response was achieved. The authors estimate that doses of 75 and 118 mg once daily would be required to maintain disease quiescence in mild and moderate cases, respectively. Adverse effects were reported in 14% and were generally mild (diarrhea, nausea, abdominal distention, and esophagitis).

Biologics

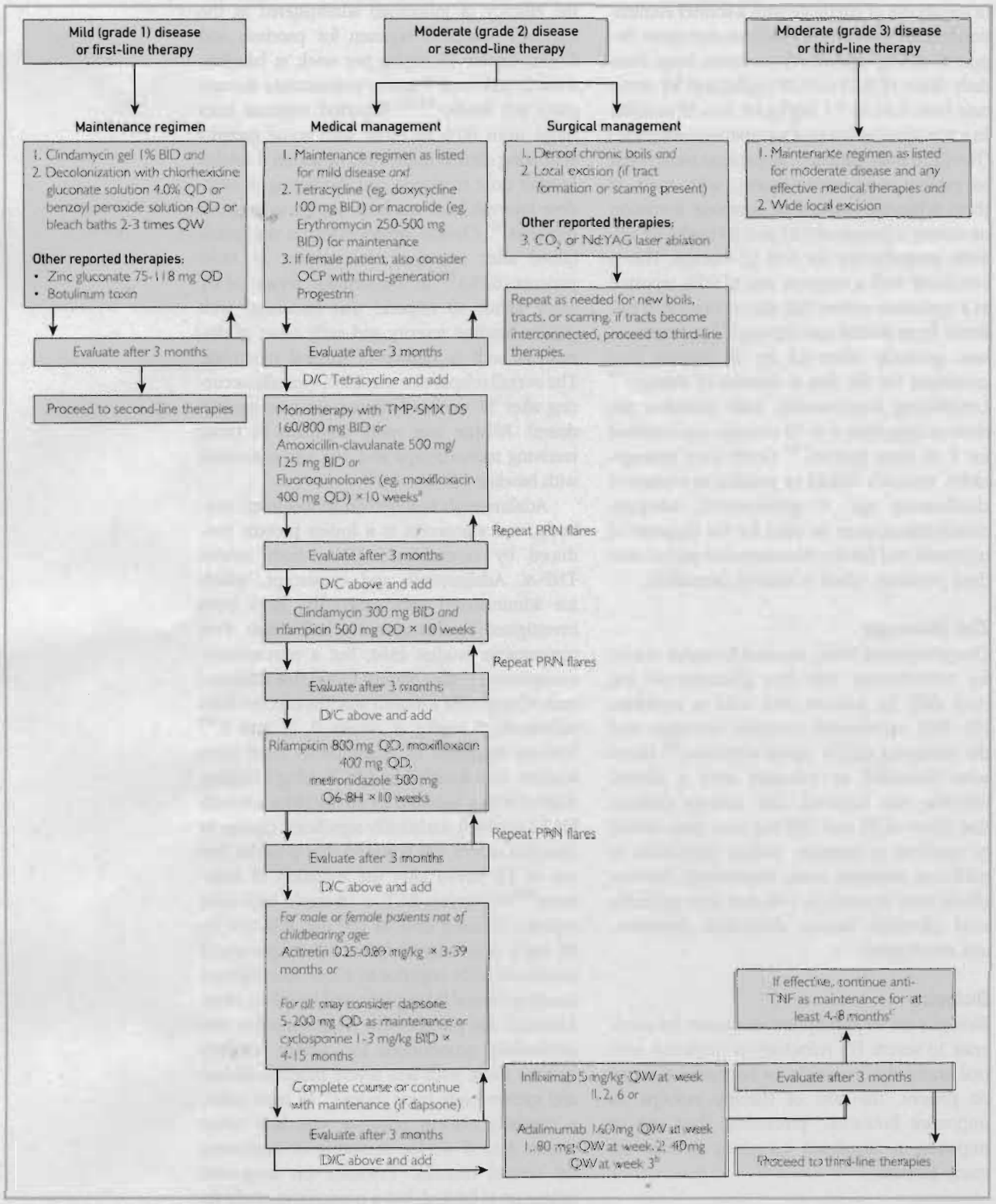
Biologics are an appropriate alternative for moderate to severe HS refractory to treatment with oral antibiotics, retinoids, or hormonal therapy. At present, the cost of therapy remains an important limitation, precluding their use or imposing a significant economic burden for many patients.

Tumor Necrosis Factor α Blockade

Infliximab is a chimeric monoclonal antibody directed against TNF-α. Case reports and a double-blind, placebo-controlled trial attest to the efficacy of infliximab administered as the standard induction regimen for psoriasis and Crohn disease (5 mg/kg per week at baseline, week 2, and week 6 and/or maintenance therapy every 4-8 weeks).[81-83] Reported response rates range from 80% to 89%, with some patients exhibiting clinical improvement within 8 weeks. Further dose escalation and shortening of interdose intervals have not been shown to improve response.[81] Clinical improvement is not maintained after cessation of treatment in most patients (62%).[83] In a systematic review of 61 cases, failure to respond was associated with greater baseline severity and early onset of disease, as well as history of surgical treatment. The overall relapse rate was 25%, typically occurring after 37 weeks of continuous treatment (6 doses). Relapse was more common in those receiving monotherapy and was also associated with baseline HS severity.[81]

Adalimumab is a human monoclonal antibody, and etanercept is a fusion protein produced by recombinant DNA; both inhibit TNF-α. Adalimumab and etanercept, which are administered subcutaneously, have been investigated as alternatives to infliximab. Few comparative studies exist, but a retrospective comparative study (N=10) found that adalimumab 40 mg twice a month was less effective than infliximab 5 mg/kg at weeks 0, 2, and 6.[84] Various regimens of adalimumab have been studied. In a double-blind RCT using a loading dose of 80 mg followed by 40 mg twice a month for 12 weeks, a statistically significant change in Sartorius scores was reported after 6 weeks, but not at 12 weeks after the initiation of treatment.[85] In another RCT, a 16-week, high-dose regimen (loading dose of 160 mg, followed by 80 mg 1 week later and then 40 mg per week) was found to be superior to a low-dose regimen (loading dose of 80 mg, followed by 40 mg twice a month) and placebo. The treatment effect was particularly pronounced for current smokers and for those with less severe baseline disease and greater body mass index.[86] In most cases, a clinically evident response was first noted within 4 to 6 weeks, persisting or improving for several months. Evidence on long-term follow-up is limited, but a prospective study reported a decrease in the efficacy of adalimumab at the 2-year mark.[87]

One double-blind RCT and several prospective trials and case reports have



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investigated varying regimens of etanercept, with mixed results.[88-91] Dosing regimens varying from 25 to 100 mg once a week for 3 months to over 1 year have been tested. A systematic review reports a moderate to significant (>50%) response in 56% of patients.[78]

Follow-up in most studies is insufficient to assess potential for inducing long-term remission. The incidence of adverse effects is comparable to that seen for other patient populations using TNF inhibitors (7.6%). Although short-term studies do not suggest an increased risk of malignant neoplasms, TNF inhibitors should be used with caution in this population, given the increased incidence of malignancy.[92,93]

IL-1 Blockade

Anakinra is a recombinant receptor antagonist that competitively inhibits the biological activity of the proinflammatory cytokines IL-1α and IL-1β. Its efficacy in HS has been reported in an open label study, in which all (N=5) patients who completed an 8-week course of anakinra 100 mg once daily reported significant decreases in their Sartorius scores.[94] The efficacy of anakinra remains to be evaluated in an RCT.

IL-12 and IL-23 Blockade

A few case reports attest to the efficacy of ustekinumab (overall response rate of 75%), a monoclonal antibody directed against IL-12 and IL-23, which is approved for the treatment of moderate to severe plaque psoriasis.[95-97]

Other Immunosuppressive Agents

Other agents investigated for use in HS include methotrexate, colchicine, cyclosporine, and dapsone. Of these, only the last 2 have reported efficacy in a few case reports. Dapsone monotherapy at doses ranging from 5 to 200 mg once daily produced clinical improvement and was well tolerated in 38% to 100% of patients (overall 56%), most of whom had mild disease. Clinical improvement was typically evident within 2 to 12 weeks and sustained only during active treatment.[78,98-100] Because dapsone is nonteratogenic and typically well tolerated, it may be a favorable option in women of childbearing age. Before the initiation of the treatment, a glucose-6-phosphate dehydrogenase level should be checked owing to the risk of hemolysis. Reports of successful use of cyclosporine have been published for a handful of patients. Dosing schedules range from 2 to 6 mg/kg once daily for periods of 4 to 15 months. All patients in this small subset experienced moderate to significant clinical improvement.[101-103] There are a small number of case reports attesting to transient improvements in HS when oral corticosteroids are used alone or in combination with other agents; overall, the evidence does not point

FIGURE 2. Treatment algorithm. Therapies for our algorithm were selected on the basis of established clinical efficacy, tolerability, and potential for adverse effects. In general, we recommend an aggressive treatment approach and early surgical intervention to prevent irreversible long-term sequelae. The appropriate initial regimen should be initiated on the basis of the assessment of disease severity at presentation (Figure 1). Serial evaluation every 3 months should be performed; if disease control is adequate or significant improvement is noted, the existing regimen should be continued to its completion (when appropriate). For patients demonstrating inadequate disease control, we recommend progression through first-, second-, and third-line therapies in the order listed. More rapid progression through the algorithm (eg, early surgical intervention) may be indicated for patients with high-risk features. Other experimental therapies not listed (eg, anakinra) may be attempted for disease that is refractory to these agents. Maintenance therapy should be continued even when more aggressive medical or surgical therapies are initiated. [a]The recommended treatment times in our algorithm are based on the average time to maximal response in clinical studies. There are no studies that systematically assess the safety and efficacy of the long-term antibiotic treatment. For patients with more severe disease, clinicians may opt to continue oral antibiotic treatment for a longer period of time. We recommend continued use of topical antibiotics in all patients as part of a maintenance regimen. [b,c]Immunogenicity is a known complication of biological therapy and is associated with a progressive decrease in treatment efficacy. Combination therapy with methotrexate (although MTX has not been shown to be effective in hidradenitis suppurativa[119]) has been shown to reduce the immunogenicity of tumor necrosis factor inhibitors in the treatment of rheumatoid arthritis, Crohn disease, and spondyloarthritis, and as such, could be considered.[120] At present, there is no evidence to suggest whether abrupt discontinuation of anti–tumor necrosis factor therapy or gradual tapering of doses produces a more sustained treatment response. In most studies, treatment is discontinued without a taper. BID = twice daily; D/C = discontinue; DS = double strength; MTX = methotrexate; Nd:YAG = neodymium-doped yttrium aluminum garnet; OCP = oral contraceptive; PRN = pro re nata, as needed; QD = once daily; QW = every week; Q6-8H = every 6 to 8 hours; TMP/SMX = trimethoprim-sulfamethoxazole; TNF = tumor necrosis factor.

to a clear role of routine use of oral or intravenous corticosteroids in the short- or long-term management of HS.[102,104,105]

Neurotoxins

The efficacy of botulinum toxin in the treatment of HS has not been systematically assessed, but scattered case reports attest to its efficacy, with reported induced remissions lasting up to 10 months.[106,107]

SURGICAL APPROACHES

Laser Surgery

In a prospective, randomized, within-patient, controlled trial, treatment with 4 monthly sessions of neodymium-doped yttrium aluminum garnet laser, along with topical benzoyl peroxide and clindamycin, was found to be superior to that with topical benzoyl peroxide and clindamycin for moderate to severe HS.[108] These findings are supported by another prospective RCT in which an overall 65.3% decrease in HS severity was reported for anatomic sites treated with 3 monthly sessions of neodymium-doped yttrium aluminum garnet laser.[109] The efficacy of carbon dioxide laser excision with marsupialization or healing via primary or secondary intention is reported by several case series, with recurrence rates at surgical sites or immediately adjacent areas ranging from 1% to 22%.[110-114] Studies comparing the efficacy of these 2 techniques are lacking.

Excisional Surgery

Surgery is an important part of the therapeutic armamentarium for HS. Conservative surgical options for milder cases include incision and drainage of boils and deroofing of chronic lesions and associated sinus tracts[115]; the latter has proved to be superior to incision and drainage in terms of recurrence rates.[115] Severe HS is treated via limited local or radical wide excision followed by primary closure, healing by secondary intention, flap advancement (skin, myocutaneous, and fasciocutaneous), or grafting. Optimal surgical techniques remain a source of controversy, and discussion of the merits and pitfalls of these reconstructive techniques is beyond the scope of this review. However, evidence suggests that the selection of a wound closure method should be guided by consideration of the size and location of the defect and laxity of the surrounding skin.[116] Several authors have suggested that the risk of recurrence is more dependent on the breadth of surgical excision and extent and duration of the disease rather than on the type of closure, suggesting that early surgical intervention after failure of noninvasive therapies may be an important goal in treatment.[116-119] Overall, most patients (~91.3%) experience partial or complete recovery with these techniques.

MANAGEMENT OF PAIN

Pain is a prominent feature of HS, thought to result from both sequelae of ongoing inflammation and the associated depression. No studies have evaluated the efficacy of different pain control regimens in HS. Scheinfeld[120] proposed a combination of both oral and topical agents, including lidocaine 5% ointment, diclofenac 1% gel, and ice packs, as well as nonsteroidal anti-inflammatory drugs, atypical anticonvulsants such as gabapentin and pregabalin, and serotonin-norepinephrine reuptake inhibitors such as duloxetine.[120]

MANAGEMENT OF PSYCHOSOCIAL SEQUELAE

No optimal strategy for managing the psychosocial sequelae of HS has been defined, but patient interviews suggest that referral to patient support groups or forums, such as those found at the Hidradenitis Suppurativa Foundation website (www.hs-foundation.org), may assist in coping.[14] Patients with symptoms of depression or experiencing impairments in social, work, or sexual functioning should be referred for counseling.

TREATMENT ALGORITHM

We propose an algorithm for treating HS on the basis of our interpretation of the available clinical evidence (Figure 2).[121,122] Our algorithm provides physicians with a layout of sequential therapies, including reasonable time frames for which a clinical response can be expected for each regimen based on estimates from the literature. We recommend a global baseline assessment (Table 2) and stratification of patients based on Hurley stages (Table 1 and Figure 1). Baseline and subsequent photographs are highly recommended for monitoring clinical progression.

The initiation of targeted HS therapies should be paired with optimization of control of

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associated comorbidities (eg, diabetes mellitus and PCOS), initiation of aggressive therapies to address modifiable risk factors, and referral for management of psychological sequelae. In the event of treatment failure, we encourage rapid progression to the next set of treatments, and for patients with high-risk features, the clinician may consider bypassing initial treatments that are unlikely to work and may result in further disease progression in the interim. A multidisciplinary approach is preferred, with close collaboration with dermatologists and surgeons to prevent progression to advanced disease and its attendant complications.

AREAS OF CONTROVERSY AND UNCERTAINTY

Effect of Early vs Late Intervention

The basis for recommending early aggressive therapeutic intervention remains hypothetical because the natural history of HS is still poorly understood. Although it is hypothesized that untreated or poorly controlled disease is accompanied by a gradual destruction of cutaneous architecture that leads to progression and irreversible sequelae, there is a need for additional studies to further elucidate the natural history of HS as well as predictors of persistent or more severe disease. In particular, longitudinal studies comparing outcomes between patients with early and late intervention or between patients with more and less aggressive therapeutic approaches are needed.

Cancer Risk

To date, only one retrospective study has assessed the risk of malignancy in patients with HS, suggesting that HS is associated with an overall 50% increased risk of developing any cancer.[7] Additional studies are needed to delineate risk factors for cancer development in diverse populations of patients with HS as well as optimal screening regimens.

Hidradenitis Suppurativa as a Systemic Disease

Isolated case reports have noted associations between HS and various conditions, including inflammatory bowel disease; spondyloarthropathy; pyoderma gangrenosum; pseudoangiomatous stromal hyperplasia syndrome; pyogenic arthritis, pyoderma gangrenosum, acne, and HS syndrome; synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome; pachyonychia congenita; Adamantiades-Behcet disease; and keratitis-ichthyosis-deafness syndrome, in addition to obesity and metabolic syndrome.[1,23,124] These associations beg the question of whether HS is a systemic disease. Although the data linking HS with obesity and metabolic syndrome are well-founded, more rigorous controlled studies are required to assess the veracity of associations between HS and these various other conditions. A recent review

TABLE 2. Baseline Disease Assessment[a,b]

Variable	Evaluation criteria	Supplementary recommendations
Baseline disease assessment	Disease severity (see Figure 1) Obtain a baseline photograph Obtain laboratory parameters (CBC count, ESR, and CRP level)	See Figure 2
High-risk features	Male sex Duration >15 y Smoking >15 pack-year history Possible high-risk features: Presence of follicular lesions Previous or current severe acne Atypical typology Axillary or perianal disease	Consider a more aggressive approach through the therapeutic algorithm
Lifestyle factors	Smoking Obesity Clothing	Consider referral to dietician or support services for weight loss and smoking cessation
Comorbidities	Diabetes mellitus Polycystic ovarian syndrome	Optimize disease control and consider administering metformin
Psychological well-being	Assess functional capacity and quality of life Screen for depression and anxiety	Support group referral highly recommended for all patients Consider referral to psychiatry
Pain control	Assess frequency and severity of pain and effect on quality of life	Administer topical analgesics Supplements with NSAIDs or other oral therapy, if necessary

[a]CBC = complete blood cell; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NSAID = nonsteroidal anti-inflammatory drugs.

[b]Baseline screening of patients should include assessment of the 6 domains listed above. The presence of high-risk features may justify a more aggressive approach with a more rapid progression through the treatment algorithm in the event of treatment failures. Optimization of comorbidities and lifestyle modification are crucial components of treatment and should be discussed at length with patients, with secondary referral to specialists as deemed necessary. Given the tremendous effect of HS on quality of life, evaluating and addressing psychosocial well-being and pain control are other critical components of the treatment.

suggested that these associations must be investigated further but may point to a common genetic or environmental trigger or shared inflammatory pathway.[123] If this is the case, additional studies may prove that certain treatment strategies are more efficacious for patients with different overlap syndromes.

CONCLUSION

A growing literature has led to an increased understanding of HS, but many questions remain. The pathogenesis remains poorly understood; current research suggests an interplay between multiple genetic, immunological, behavioral, and endocrine factors. Likewise, although the therapeutic armamentarium of HS includes various treatments, a large number of these treatments have not been systematically assessed in randomized placebo-controlled trials. In addition, there are few comparative studies of efficacy of treatments in different pharmaceutical classes. At present, the sum of the evidence seems to suggest that a multimodal approach may be most effective for most patients, incorporating both medical and surgical treatments in addition to lifestyle modification. Future studies should also attempt to determine whether certain phenotypic factors are associated with differential responses to certain treatments. These data will tremendously advance the evidence base for the treatment of HS and hopefully lead to minimal homogeneity in treatment practices and optimal outcomes for patients struggling with this debilitating and difficult-to-treat disease.

Abbreviations and Acronyms: **CPA** = cyproterone acetate; **HS** = hidradenitis suppurativa; **IL** = interleukin; **PCOS** = polycystic ovarian syndrome; **RCT** = randomized controlled trial; **TNF** = tumor necrosis factor

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