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# Drug Therapy for Hidradenitis suppurativa: An Update

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**Abstract**
Hidradenitis suppurativa (HS) is a chronic, suppurative debilitating skin disease characterized by the presence of polymorphic recurrent inflammatory lesions with a malodorous discharge mainly distributed in the flexural and friction prone areas. The global prevalence of HS is about 4% with a 3:1 female to male ratio. With a pre-pubertal onset, it usually affects young individuals in their early twenties. With its chronic and recurrent course, HS leaves a debilitating impact on an affected individual's quality of life. The HS has a multifactorial etiology and the pathogenesis is unclear. Currently, there are several therapeutic options (antibiotics, retinoids, biologic and immunosuppressive agents) available which can only provide symptomatic relief for a transient time, but there is no definite cure for HS. Currently, dermatologists from all around the world face a stern challenge to find the right therapeutic combination in order to provide long lasting remissions to the affected individuals. In this review, we discussed different medical therapeutic options currently available for treating HS.
**Keywords** Hidradenitis suppurativa, acne inversa, Verneuil's disease, smoker's boils.

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## Introduction

Hidradenitis Suppurativa (HS) is a chronic, suppurative, inflammatory skin disease of the apocrine gland bearing skin. It clinically manifests as recurrently occurring painful nodules and abscesses, which gradually progress to form sinus tracts and fibrotic scars. It predominantly affects inverse body sites such as the axillae, inguinal, gluteal and inframammary areas. Hence, it is also known as acne inversa. It may also involve other body sites such as the back [1, 2]. These nodules and abscesses also discharge malodorous pus which can cause serious discomfort to the affected individual. Diagnosis is mainly clinical and there needs to be at least two episodes of these painful nodules within a span of 6 months to establish the diagnosis [3]. The HS has a global prevalence of about 4% with a predominantly post-pubertal onset in individuals in their early twenties with a 3:1 female to male ratio [4-6]. Its onset is relatively uncommon in pre-pubertal and post-menopausal individuals. However, a few instances have been reported in pediatric age group [7, 8]. The HS tends to persist for several years with frequent flares and gradually worsens with time, causing a debilitating impact on an individual's quality of life [9]. The Sartorius staging system modified from Hurley's staging system and HS physician global assessment score are used to determine the disease severity (Table 1) [3, 10,11].

The etiology of HS is unclear and seems to be multifactorial. About 35-40% of HS patients report a positive family history of HS with an autosomal dominant mode of inheritance. Mutations in gamma-secretase genes (thought to regulate epithelial cell proliferation and differentiation) have been identified and are thought to play an etiological role in a minority of HS cases [12]. Peri-pubertal onset and a decrease in HS activity in post-menopausal individuals hint the possibility of an endocrine cause [13]. The chronic and relapsing nature of HS suggests the possible involvement of certain bacteria which gradually form bio-films and remain adherent to the epithelium of the sinus tracts and hair follicles in HS [14, 15]. Obesity and smoking are considered to be the environmental factors associated with the trigger or exacerbation of HS. Obesity contributes to the severity of HS as larger skin folds are prone to sweat retention, possible maceration and friction [13, 16]. There are reports that suggest nicotine causes follicular plugging and over secretion of eccrine glands. It also induces chemotaxis of neutrophills which eventually contributes to inflammation [17-19].

The pathogenesis of HS is also incompletely understood, but mainly revolves around the follicular occlusion. Infundibular hyperkeratosis and follicular hyperplasia are considered to be the initial events which play prominent roles in follicular occlusion [20]. The subsequent event being accumulation of apocrine gland secretions and cyst formation eventually leads to hair follicle rupture and the formation of abscess. Gradually, these abscesses evolve into multiple sinus tracts and extensive scars [21, 22]. Several studies have

reported a significant increased levels of tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β and IL-10 in the lesional and peri-lesional areas of skin [23]. There's an increased expression of IL-12 and IL-23 by the macrophages of the lesional skin eventually causing buildup of IL-17 producing T helper cell infiltrate [24]. Kelly et al. [25] reported the presence of activated caspase-1 in the skin lesions which causes the production of IL-1β and IL-18. These findings indicate an active role of IL-23 / Th 17 and caspase-1 pathways in the pathogenesis of HS [23-25].

**Table 1** Hurley's staging system for evaluating disease severity in Hidradenitis suppurativa [10].

| Stages | Clinical features |
|---|---|
| I (mild) | Abscesses only, single or multiple, without sinus tracts and cicatrization |
| II (moderate) | Recurrent abscesses with tract formation and cicatrization. Single or multiple separated lesions |
| III (severe) | Multiple intercommunicating sinus tracts and abscesses throughout an entire area involved |

Over the years, a significant amount of efforts has been put in understanding HS, yet until today, there isn't any definite medical remedy for curing HS. Hence appropriate treatment of HS remains a daunting challenge for the dermatologists desperate for a cure. With this review, we would like to present a summary of various medical therapeutic options currently available for treating HS in a simplified and reader friendly manner.

## Management of HS

### Life style modification

Lifestyle modification revolves around weight loss, smoking cessation and appropriate clothing. According to the literature, the majority of the HS patients is either overweight or obese with a body mass index (BMI $\geq$ 25 kg/m$^2$) and BMI happens to be positively associated with disease severity in HS [26]. One of the studies reported a 35% decrease in the symptoms and a remarkable reduction in the number of involved body areas after patients with HS underwent bariatric surgery and achieved 15% weight loss [27]. Individual case reports also reported similar outcome after bariatric surgery [28, 29]. Hence obese or overweight patients with HS must be encouraged to lose weight as this may have a positive influence on the course and severity of HS. It is thought that cessation of smoking has a positive influence on the course and severity of HS, but currently, there is no enough evidence. In a study, it was reported that in comparison with the active smokers, non-smokers and the ones who quit smoking had shown remarkable improvement in the course and disease severity [30]. Another case report suggested improvement of symptoms in two patients upon cessation of smoking [30]. Keeping in mind the overall benefits of cessation of smoking, we think that HS patients should be encouraged to quit smoking. In regards to clothing, even though currently there is no supporting evidence, we suggest that HS patients should avoid wearing tight fitting clothes in order to avoid friction which theoretically is considered to be involved in the pathogenesis of HS.

### Topical therapy

When it comes to topical therapy, the major agents used are antibiotics and keratolytics which are suitable for the treatment of mild HS, characterized by skin lesions such as comedones, papulo-pustules or nodules. For maximum efficacy, a combination of keratolytic agent, topical antibiotic along with life-style modifications are recommended.

*Antibiotics*

Topical clindamycin (1%) is the most commonly used antibiotic for HS. Two clinical trials suggested that the application of topical clindamycin daily twice for about 3 months had a significant impact in the patients with mild HS as there was a gradual improvement in the pustules, nodules and abscesses. There may be mild burning sensation post application [31, 32].

*Resorcinol cream*

It is basically an exfoliant that has antiseptic and anti-pruritic properties. At higher concentrations, it also acts as a keratolytic agent [33]. In a small case study of about 12 patients, 10-15% of resorcinol was topically applied twice daily which resulted in a remarkable improvement in soreness and a gradual decrease in the mean duration of the nodules and abscesses [33]. It is hypothesized that, by relieving the follicular occlusion it effectively prevents the appearance of new inflammatory lesions and helps in the quick resolution of active nodules [30]. It is better to avoid during pregnancy and patients should also be advised to limit the application of resorcinol to certain body areas since it is easily absorbed [30].

### Systemic antibiotics

The chronic and relapsing nature of HS suggests the possible involvement of certain bacteria and the formation of bio-films which may have a key role in the secondary pathogenesis of HS [14, 15]. Over the years, various antibiotics have been used in the management of HS mainly due to their antibacterial,

anti-inflammatory and immune-modulatory effects. In mild HS, complete remissions are possible with long-term antibiotic treatment, but in cases complicated by scars, fistulas and fibrosis, they are hardly cured, but they can subside inflammation and improve the conditions for surgery [30].

*Tetracycline*

These are a class of broad spectrum antibiotics that inhibits bacterial protein synthesis and also exhibit anti-inflammatory effects by down-regulating the expression of pro-inflammatory cytokines such as TNF-α and IL-1β and by up-regulating the expression of anti-inflammatory cytokines such as IL-10 [34-36]. A recent survey reported that oral tetracycline happened to be the first preference for nearly 75% of dermatologists in UK [37]. Because of their anti-inflammatory effects and mild side-effects, tetracycline can be used in the long-term treatment of HS [38]. However, what concerns is their lack of efficacy in dealing with or preventing HS exacerbations and their high rate of resistance (64%) [39]**.** Side-effects include GI distress and photosensitivity [40]. Tetracycline is classic chelator and should not be taken along with diet, vitamins and mineral supplements since they bind with the ions in the gut and get ionized which means they are not absorbed and won't be able to exhibit their effects. They are contraindicated in pregnancy due to their teratogenic effects [41].

*Double antibiotic regimen*

Clindamycin is a bacterial protein synthesis inhibitor and is particularly effective against Gram-positive bacteria while most of the Gram negative aerobic bacteria show resistance to it. It also enhances chemotaxis and phagocytosis and increases the release of TNF and IL-6 [42-44]. Rifampicin is a bactericidal antibiotic as it inhibits the bacterial DNA dependent RNA polymerase. It mainly works against Gram-positive cocci, Gram-negative cocci and bacilli and anaerobes [45]. It also tends to exhibit mild immuno-suppressive properties. In the literature, there are four published studies regarding the clindamycin-rifampicin drug regimen [46-49]. A total of 164 patients received treatment with clindamycin 300 mg (twice a day) and rifampicin 600 mg/day for a total duration of 10 weeks. A total of 88 patients completed the full course of treatment while 21 patients discontinued because of GI discomfort such as nausea and diarrhea. Regarding the remaining 55 patients, no data was available. Out of the 88 patients, 25 patients (28.4%) showed complete remission while 57 patients (64.8%) showed partial response. Remaining 6 patients (6.8%) were non responsive to clindamycin-rifampicin therapeutic regimen. A maximum clinical response is usually achieved within 10 weeks and about 61.5% of relapse rates are reported upon discontinuation of the drug regimen [46-48]. One prospective study reported that 23 patients received treatment with clindamycin 300 mg (twice a day) and rifampicin 600 mg/day for a total duration of 10 weeks. 20 patients completed the full course of treatment while 3 patients discontinued. Out of the 20 patients, 17 patients had their Sartorius score reduced by 25% [49]. According to the literature, clindamycin and rifampicin work synergistically and induce a bactericidal effect on *Staphylococcus aureus in vivo* [50]. As a physician one should always keep in mind the possible drug interactions. Rifampicin is a cytochrome P450 inducer while CYP3A4, a cytochrome P450 member metabolizes clindamycin. Hence, clindamycin may be readily metabolized leading to its low serum levels [51-53]. Additionally, when both are taken orally, the bioavailability of clindamycin is further reduced since rifampicin reduces the hepatic first pass effect of clindamycin [51]. The most common adverse-effects of clindamycin-rifampicin regimen are diarrhea, nausea and vomiting [42, 54]. Orange or red discoloration of urine, tears and sputum are associated with the intake of rifampicin and it can also lead to permanent discoloration of contact lens [54]. During pregnancy, clindamycin is relatively safer to use as no congenital anomalies have been reported in the children born to females treated with clindamycin [41]. However, rifampicin must be avoided in pregnancy as there is insufficient data regarding the intake of rifampicin during pregnancy [41]. Females need to use extra birth control measures since rifampicin interferes with the oral contraceptives metabolism [54].

*Triple antibiotic regimen*

For severe or resistant HS patients, another alternative is the triple combination therapy with rifampicin, metronidazole and moxifloxacin [55]. Metronidazole is a broad spectrum antimicrobial agent which apart from anti-protozoal activity also exhibits bactericidal effects against Gram-negative anaerobic organisms [56]. Additionally, it exhibits immuno-suppressive and anti-inflammatory effects by decreasing the levels of interleukin-1β, interleukin-6, interleukin-8, interleukin-12, interferon (INF) -γ, and TNF-α and by interfering with the leukocyte migration to the site of inflammation [57]. Moxifloxacin is a fluoroquinolone that interferes with the bacterial DNA replication by inhibiting topoisomerases. It's a wide spectrum bactericidal agent that works against Gram-

positive, Gram-negative and atypical pulmonary pathogens. It also exhibits certain immunomodulatory effects by inhibiting the secretion of IL-1α and TNF-α by monocytes [58]. In one of the retrospective study, 28 patients were treated with a triple drug regimen involving rifampicin 10 mg/kg once daily, moxifloxacin 400 mg daily and metronidazole 500 mg thrice daily for a duration of 6 weeks. Out of the 28 patients, 16 patients achieved complete remission while the remaining patients showed partial response [55]. Over the years triple therapy has been yielding promising results in the treatment of HS. Metallic taste, nausea and headache are the common side effects associated with the intake of metronidazole while rarely it may also cause neurotoxicity. It can also lead to disulfiram like reactions, hence it is of utmost importance that the patients are well informed to stop alcohol intake during the treatment period [56]. Diarrhea, nausea and dizziness are common side-effects of moxifloxacin. It may also cause prolongation of QT interval, hence better to avoid combination with class IA or class III anti-arrhythmic drugs [59]. Moxifloxacin is a chelator and should not be taken along with antacids, sucralfate, food, vitamins and mineral supplements. Triple therapy is contraindicated in pregnant or breastfeeding females. Females need to use extra birth control measures since rifampicin interferes with oral contraceptives metabolism.

**Retinoids**

*Isotretinoin*

It is known for its wide array of anti-proliferative, anti-inflammatory, anti-neoplastic and immunomodulatory effects [60]. The use of isotretinoin in the management of HS is based on an outdated theory which suggested that the pathogenesis of HS and acne vulgaris are similar. However, the fact that decreases the size of sebaceous glands and its activity is considered irrelevant in the pathogenesis of HS [61]. In a systematic review of seven studies, it was reported that 174 HS patients received daily doses of isotretinoin 0.5 to 1.2 mg/kg for 4-12 months, of whom, only 32 reported obvious improvements (18%), while 30 reported moderate improvement (17%), and there was no obvious improvement in 112 patients (64%) [62]. Those patients who were responsive to isotretinoin were mostly benefitting from its immuno-modulatory effects and they all had mild HS [62]. Hence, taking into account the higher non responsive rates and teratogenic effects, we prefer to avoid using isotretinoin in treating HS.

*Acitretin*

Acitretin is an etretinate metabolite with a relatively shorter half-life. It acts by normalizing proliferation of epithelial cells, epidermal differentiation and epidermal cornification by influencing the hyperkeratosis of the infundibular follicular epithelium [63]. A retrospective study reported that 12 patients with severe HS received daily doses of acitretin 0.25 to 0.88 mg/kg for 9 to 12 months. Complete remission was observed in nine patients while mild-moderate clinical response was observed in the remaining three patients. However, all patients complained of cheilitis during the course of treatment [63]. Recently, an open label trial, reported that 17 patients with severe HS received daily doses of acitretin 0.5 to 0.6 mg/kg for up to 9 months. Nine patients completed the full trial of acitretin treatment, of whom, 8 achieved remarkable improvement with a 50% reduction in the Hidradenitis suppurativa disease severity score (HSSI). Some patients discontinued mainly due to lack of improvement or side effects [64]. In contrast to isotretinoin, acitretin has shown promising results in the management of HS. Due to its teratogenic effects, its use must be avoided in females of childbearing age. If prescribed, females should be well counseled regarding the need for an adequate conception during the course of the treatment and must continue contraception up to 24 months post cessation of the therapy since in the presence of ethanol, acitretin gets converted to etretinate, which requires about 24 months for complete elimination from the fatty tissue [65]. Teratogenicity, side effects and most importantly higher risk of recurrence post cessation of therapy limit its long-term usage.

*Alitretinoin*

It is another systemic retinoid with a mode of action similar to acitretin, but with a relatively short half-life. Hence, it would be a preferable drug for female HS patients. In a recent study, a total of 14 patients received daily treatment with alitretinoin 10 mg for a duration of twenty four weeks. Six patients showed remarkable improvement with a 50% reduction in the Sartorius score. Improvement was also observed in other five patients; however, with a $\leq$50% reduction in the Sartorius score while three patients were non-responsive [66]. However, females need to continue with adequate contraception up to 1 month post cessation of the therapy.

**Biologics**

They are a group of new agents currently being used as an alternate therapy to provide longer remission periods in situations where moderate-severe HS is non-responsive to retinoids, oral antibiotics and

hormonal therapy. However, with the use of TNF-α inhibitors, patients are prone to easily develop rhinitis, UTI's (urinary tract infections), URTI's (upper respiratory tract infections) and bronchitis [72, 73, 77]. Prior to the onset of treatment, a TB screening test must be done for all patients due to the known risk of TB associated with the use of TNF-α inhibitors. Patients with underlying medical conditions such as heart failure, hepatitis B and various malignant neoplasms should be excluded [73, 78]. The use of biologics is contraindicated in pregnant and lactating females. Female patients must be advised to take adequate contraceptive measures for at least five half-life post the intake of last dose [3, 73, 78].

*Infliximab*

Infliximab is a monoclonal antibody that targets tumor necrosis factor–alpha (TNF-α). It's a human IgG with a fragment of the antigen binding (Fab) portion that specifically binds to the soluble and trans-membrane TNF-α and in-turn prevents *TNF-α* from binding to its receptors [67]. Several studies have been published evaluating the clinical efficacy of infliximab in the treatment of HS. Usually, a standard induction regimen of 5mg/kg (as used in psoriasis and Crohn disease) is administered at week 0, second week and the sixth week with a maintenance dose every 8 weeks [68-70]. The significant clinical response has been reported during the infliximab therapy as remarkable clinical improvement was observed in some patients as early as 8 weeks. However, there is a high recurrence in about 25% to 50% of the patients after 37 weeks of continuous infliximab therapy [68, 69, 71]. It is advised that an eight week gap is probably quite long for HS patients since usually around 6 weeks after infusion, patients complain of gradual increase in the number of inflammatory lesions and may be a 4 week gap is more preferable in terms of efficacy [71]. However, Deckers et al. [30] suggested that a 6 week interval is more suitable since shorter intervals for infliximab infusions generally lead to severe side effects and added economic burden for the patients. Generalized urticaria and anaphylactic shock may develop in some patients after infliximab infusion [72].

*Adalimumab*

It is a monoclonal antibody that targets tumor necrosis factor alpha (TNF-α). It attaches to the soluble TNF-α and in-turn prevents the binding of TNF-α with TNFR1 and TNFR2 receptors. Additionally, it alters the levels of adhesion molecules required for the leukocyte migration and it also decreases the plasma concentrations of IL-6 and C- reactive protein (CRP) [73]. Adalimumab is an alternative to infliximab and one of the comparative retrospective study reported that 40 mg adalimumab administered at alternate weeks (monthly twice) was less effective than infliximab 5mg/kg administered at baseline, week 2 and week 6 [74]. Two prospective studies reported using 40 mg adalimumab every alternate week for duration of 12 weeks. Initially after 6 weeks of treatment, there was significant clinical response. But at the end of 12 weeks, there was no significant difference when compared with the baseline or with the placebo. Moreover, higher rates of recurrence were seen after the cessation of therapy [75, 76]. Another large prospective placebo controlled trial reported 40 mg adalimumab on a weekly basis was more effective than 40 mg adalimumab administered on alternate weeks or placebo after treatment duration of 16 weeks. In the weekly administered group, only 18% of the patients achieved moderate to mild clinical response. There was a significant drop in the clinical response when for 16 weeks 40 mg adalimumab was given on alternate weeks. Hence, a high dose regimen is needed to achieve a significant clinical response in HS patients [77].

*Etnarcept*

Etnarcept is a fusion protein that binds and neutralizes the trans-membrane tumor necrosis factor (TNF), soluble TNF and lymphotoxin. Additionally, it alters the emigration of neutrophills, T lymphocyte and dendritic cells [78]. In a prospective study, 10 patients were weekly treated with 50 mg etanercept subcutaneously for a total of 12 weeks. A $\geq$50% reduction in the disease activity was observed in 6 patients and this effect lasted for another 12 week follow-up period [79]. However, similar results couldn't be obtained in other open-label and placebo controlled studies. In another open-label trial, a total of 15 patients received weekly treatment with 50 mg etanercept and only 10 patients could complete the 12 week therapeutic courses. Three patients showed a decrease of 50% in the Physicians Global Assessment (PGA) score [80]. In a placebo controlled trial, 10 patients received twice a week, 50 mg etanercept while another 10 received placebo for about 12 weeks. After the completion of the trial, there wasn't any statistically significant difference between the two groups [81]. Hence, we need further studies as evidence to determine the therapeutic benefits of etanercept in the treatment of HS.

*Anakinra*

It is an IL-1 receptor antagonist that competitively suppresses the inflammatory effects of pro-inflammatory cytokines interleukin-1α and interleukin-1β which happen to be present in the skin lesions and the surrounding skin [82, 23]. To date, a total of 10 patients have been treated with anakinra with a mixed outcome [83-87]. Seven patients demonstrated remarkable improvement in the skin lesions [83, 84, 87] while the other three patients were non responsive [85, 86]. Further studies are needed to assess and confirm the efficacy of anakinra in the management of HS.

*Ustekinumab*

It is a combined inhibitor of interleukin-12 and interleukin-23. It's a monoclonal antibody that targets the p40 subunits of interleukin-12 and interleukin-23, thus preventing them from binding to their receptors [88]. To date, a total of eight patients with HS received treatment with 45 mg ustekinumab subcutaneously at baseline, week 4 and week 12 and at regular intervals of 3 months. Complete remission was observed in four patients while three patients showed partial remission and one patient was non-responsive to ustekinumab treatment [89-92]. Recently, an open label study reported that a total of 17 patients received treatment of 45 to 90 mg ustekinumab subcutaneously at baseline, week 4, week 16 and week 28. In the end, 12 patients completed the therapy. Six patients achieved $\geq$50% decrease in their modified Sartorius scores at week 40, while eight patients achieved 25% to 50% decrease in their modified Sartorius scores and 5 patients discontinued due to inefficacy, side effects, and / or psychological problems [93]. Currently, the results of ustekinumab seem to be promising. However, further clinical trials are required to evaluate and verify the efficacy of ustekinumab in the treatment of HS.

**Other Immuno-suppressive agents**

*Systemic and intra-lesional corticosteroids*

Systemic corticosteroids are widely used to control acute HS flares mainly due to their immunosuppressive and anti-inflammatory effects. In order to limit the long-term complications, a dosage of 0.5-0.7 mg/kg is recommended for short term treatment of acute flares and over the time it should be gradually tapered [3, 94]. Intra-lesional steroids are one of the most preferable therapeutic options in the management of HS since they have a rapid clinical response within 48 to 72 hours. Intra-lesional triamcinolone acetonide 5 to 10 mg/ml is commonly used in the management of acute flares of a solitary or limited number of abscesses. It is also helpful in the treatment of recalcitrant nodules and sinus tracts [3]. Usually, there are no systemic side effects at the recommended doses; however, there may be local cutaneous changes such as atrophy, pigmentary changes and telangiectasia, and super infections may be undesirable complication [95].

*Dapsone*

It is not only known for its antimicrobial and antifungal effects, but also for its considerable anti-inflammatory effects. Additionally, it is also known to suppress interleukin-8 and tumor necrosis factor-α level [96]. In a study, 24 patients with HS received daily doses of dapsone 50-200 mg for 48 months, of whom nine patients showed clinical improvement, whereas 15 patients were non-responsive to dapsone therapy [97]. In another small prospective study, five refractory HS patients received dapsone 50 to 200 mg/day and significant improvement was observed in all patients after 4-12 weeks of treatment [98]. It can be prescribed for females of childbearing age since it is non teratogenic and well tolerated. However, glucose-6-phosphate dehydrogenase (G6PD) levels should be checked prior to the initiation of the therapy due to the possible risk of hemolysis [12].

*Fumarates*

It exhibits anti-inflammatory and immune-regulatory effects. They also interfere with the production of interleukin-12 and interleukin-23 by the antigen presenting cells (dendritic cells and macrophages) [99]. In a small prospective pilot study, seven patients with moderate to severe HS received treatment with daily doses of fumarates 720 mg/day as a last resort therapy. After 20 weeks of treatment, gradual improvement was observed in one patient, while two others reported faster resolution of lesions and inflammation. However, four patients discontinued the treatment as there was no significant improvement. After four months of treatment, another one discontinued due to persistent diarrhea. Two patients tolerated up to one year with significant improvement [100].

*Cyclosporine*

It is a calcineurin inhibitor and a potent immunosuppressive agent [101]. It downregulates the production of IL-2 and targets lymphocytes and macrophages of the epidermis and dermis. Additionally, it inhibits keratinocytes, T lymphocytes, antigen presenting cells (APC) and natural killer cells (NKC) [101]. A handful of cases have been published in regards to the use of cyclosporine in the treatment of

HS. For example, there was a significant improvement in four patients with recalcitrant HS after daily treatment with cyclosporine 3-5 mg/kg for about 6 weeks to 4 months [102 – 104].

**Hormonal therapy**

Frequent post pubertal onset, pre-menstrual worsening and improvement during pregnancy in female HS patients raises a doubt regarding the role of hyper-androgenism in the pathogenesis of HS [105-107]. However, with the absence of clinical virilism and abnormal serum hormone levels, the significance of hyper-androgenism in HS pathogenesis was dismissed [108].

*Finasteride*

Finasteride is a 5α-reductase inhibitor that halts the conversion of testosterone to the more potent dihydrotestosterone [109]. It is a treatment modality for benign prostatic hypertrophy and androgenic alopecia in males. In the literature, the use of finasteride has been documented in 12 HS patients of varying ages. Good clinical response was noted in seven patients who received finasteride 5 mg daily for the duration of about 2 to12 weeks [110, 111]. Recurrence was seen in two patients, one month after the cessation of finasteride therapy. Considerable improvement was noticed in four female children who received daily treatment with 1.25 to 10 mg of finasteride along with oral contraceptives, antibiotics and / or surgery [111, 112]. Decreased libido and gynecomastia are the most common side effects in males. The use of finasteride should be avoided in pregnant females due to the possible risk of male fetus being feminized [109].

*Cyproterone acetate*

Cyproterone acetate exhibits anti-androgenic effects by binding to the testosterone receptors and in-turn inhibits the androgen biosynthesis. One study reported good clinical response in 12 out of 18 patients after using ethinyloestradiol 50 µg\cyproterone acetate 50 mg and ethinloestradiol 50 µg/norgestrel 500 µg [113]. However, large clinical trials are required to verify their efficacy in the management of HS.

**Other therapeutic options**

*Metformin*

It is an insulin sensitizer and happens to be the first line therapeutic option for type 2 diabetes mellitus [114]. A recent prospective study reported that 25 patients with mild HS received up-titrated doses of metformin 1.5 mg/day for 24 weeks, among those, a significant improvement was observed in 18 patients and seven patients achieved a remarkable improvement with a total decrease of $\geq$50% in the Sartorius score. Remaining seven patients showed no response to metformin therapy. Patients complained of mild gastro-intestinal distress after the onset of therapy [115]. Metformin improves utilization of glucose by lowering the production of glucose, increasing insulin sensitivity and by enhancing the uptake of peripheral glucose. It is also reported to exhibit anti-androgenic and anti-oxidant properties. Since hyperandrogenism and diabetes are contributory factors in HS, the use of metformin in treating mild HS seems to be promising [2].

*Zinc gluconate*

One of the study reported that 22 patients with mild to severe HS were administered with 90 mg of zinc gluconate daily. A total of eight patients showed complete remission while the remaining 14 patients showed partial remission. Doses were gradually tapered after achieving a stable clinical response. It is better to maintain doses between 75 and 118 mg once daily in order to prevent relapses. Four patients experienced minor gastro-intestinal discomfort [116]. Zinc acts by altering the differentiation and function of T cells. Additionally, it also activates natural killer cells (NKC) eventually leading to an increased secretion of IL-6, IL-1β and TNF-α [117].

*Botulinum toxin*

Its role in the treatment of HS is currently unknown. A handful of case reports have shown good clinical response with remissions lasting up to 10 months [118, 119]. It is speculated that by reducing the moist environment, it in-turn affects the bacterial growth [120].

*Analgesia*

Since pain is a prominent feature of HS, adequate pain management is of utmost importance in the treatment of the HS [121]. In the literature, there aren't any studies describing the use of analgesics in HS. Oral acetaminophen 1000 mg, four times a day can be given to patients complaining with moderate constant pain since it is well tolerated [121]. However, one must be cautious regarding the possible hepato-toxicity associated with excessive doses of acetaminophen. If there is no improvement in pain, then non-steroidal anti-inflammatory drugs (NSAID) can be used. However, there isn't any evidence suggesting the superiority of one NSAID over another [122]. The use of various NSAIDs solely depends on the clinical

experience of the physician. However, proton pump inhibitors must be prescribed for patients taking NSAIDs on a frequent and long-term basis due to the given risk of acquiring gastric ulcers. Opiates are considered for patients with significant long-term pain [3]. However, they have a possible risk for addiction, hence short term is preferable. Other preferable agents that can relieve pain include topical 5% lidocaine ointment, 1% diclofenac gel, ice packs, gabapentin, pregabalin and duloxetine [121]. They can be used as a mono or combinational therapy.

## Conclusions

Currently, several therapeutic options are available, but none of these provide definite cure. For mild HS (Hurley stage I), the topical application of clindamycin and resorcinol cream +/- oral tetracycline are recommended. In cases with moderate to severe HS (Hurley stage II and III), systemic antibiotics (tetracycline or clindamycin-rifampicin regimen or metronidazole-moxifloxacin-rifampicin regimen) are usually effective in decreasing the number of inflammatory skin lesions. However, in cases with no improvement or frequent recurrences, acitretin can be opted for long-term management. Due to the associated teratogenicity, its use is limited in females of childbearing age. If patients are still non-responsive to antibiotics and retinoids then we need to switch to biologics. Biologics include TNF-α inhibitors (infliximab and adalimumab) etnarcept, anakinra and ustekinumab. Medical treatment should be combined with other physical interventional therapies and lifestyle modifications. Further large scale studies and trials are required to evaluate the efficacy of hormonal therapy and drugs such as dapsone, cyclosporine, metformin and zinc gluconate in the management of HS. HS is relatively difficult to treat and Hurley staging comes handy in determining the choice of treatment.

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