

Expert Opinion

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Medical treatment of hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a common skin disease affecting an estimated 2% of the population. It causes significant symptoms and is notoriously difficult to treat. In this article, the current medical therapy is reviewed. At the present time, therapy appears to be based on an interpretation of the disease as either infectious or a form of acne. The understanding of the pathogenesis of HS suggests that these are not adequate models in order to understand the disease and this may explain the insufficiency of currently available medical treatment. The literature is sparse and there is a shortage of randomised, controlled trials. Three small, randomised, controlled trials have suggested that clindamycin, tetracycline and oestrogens and cyproteroneacetate may have an effect in some patients. Preceiving HS as an inflammatory skin disease suggests the use of general immunosuppressive drugs in the treatment of this condition. This approach, using both traditional immunosuppressants and monoclonal antibodies, has been assessed in a small number of patients and appears to have some potential. However, the main source of evidence for this are case series and there is a strong need for more formal studies in this potentially debilitating disease.

Keywords: antiandrogens, clindamycin, hidradenitis suppurativa, immunosuppressants, infliximab, quality of life, retinoids, skin disease, systemic therapy, tetracycline, topical therapy

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1. Introduction

Hidradenitis suppurativa (HS) is a common, disabling dermatosis with a profound impact to patients quality of life [1,2]. The clinical presentation of the disease is characteristic and allows simple diagnosis. It has been suggested that HS be described as inverse recurrent suppuration (IRS) as this sums up its clinical presentation of recurrent lesions clinically resembling boils, unresponsive to conventional therapy, located to inverse areas. The lesions are not cystic as with boils, which explains the lack of effect of simple lancing, nor do the patients have lesions outside inverse areas. Clinically HS has three stages:

- **Primary stage:** boils appear in separate places and where nodular non-inflamed precursor lesions appear as well.
- **Secondary stage:** sinus tracts appear with scarring linking individual lesions.
- **Tertiary stage:** coalescing, scarring and sinus tracts predominate although inflammation and chronic discharge also appear.

The disease causes symptoms. Patients are frequently bothered by pain, scarring, recurrent discharge and smell from the lesions [2-4]. It is easy to imagine the impact of the disease on the lives of patients and it has been shown to have a high impact on their quality of life [2].

The aetiology of the disease remains unknown, but it is a disease of the hair follicles of the inverse areas of the body, predominantly the axillae and the genitofemoral areas. Bacteria are present in a minority of lesions and known pathogens such as *Staphylococcus aureus* occur only in a minority of lesions. The disease is therefore related

to other follicular diseases, such as acne or pilonidal sinus tracts, although they are not identical. The pathogenesis is thought to involve inflammation of diseased follicles and the subsequent formation of draining sinus tracts which form the histological main feature of the disease [5]. It has been suggested that specific cells are recruited from the hair follicle epithelium to form sinus tracts following inflammation [6].

The treatment of HS remains a challenge. Surgical therapy, including laser therapy and possibly photodynamic therapy, are considered curative by some, but may involve large excisions associated with cost and comorbidity [7-9]. In addition, the disease is a multifocal disease often involving several lesions in several different regions. The multifocal nature of the disease strongly suggests that a systemic form of therapy would be more advantageous to the patients than focal destruction or surgery. There is, therefore, an immediate and considerable need for suitable medical therapy for this distressing disease.

2. Goal of therapy

The goal of medical therapy in HS is to heal existing lesions and prevent the development of new lesions in the areas potentially affected by the disease (i.e., the axillae and groin). As the lesions are dominated by scarring, the healing of existing lesions is more difficult to achieve than prevention. Therefore, the treatment should primarily prevent the appearance of early lesions and ideally, allow regression of secondary changes such as scarring and sinus tracts.

3. Current best practice

Guidelines have been suggested for the treatment of HS but are most likely to have a limited impact on this common disease, which is treated by a variety of specialities. Current best practice was therefore sought in the literature. A review was carried out with the aim of identifying medical interventions in HS. Papers describing surgical procedures, laser therapy or photodynamic therapy were not included. EMBASE and PubMed were searched for papers on 'Hidradenitis suppurativa, hidrosadenitis suppurativa or acne inversa'. Papers describing therapy in neutrophilic eccrine hidradenitis were not included. Papers were classified according to the strength of the evidence presented and the information extracted. Because of the quantitative and methodological weaknesses of the available studies, the extracted data are cautiously discussed in general terms, rather than displayed in tables or figures in order to avoid inappropriate overinterpretation. Single observations may generate a hypothesis, but are difficult to use as the basis of general treatments strategies.

The availability of papers on the subject of HS was very limited. Only three papers described randomised, controlled trials and one paper reporting an intermediate-sized, open case series. The majority of papers contained only small open series or cases.

Clinically, the most disturbing symptom of HS is the formation of primary lesions clinically resembling boils, which are commonly associated with infection and bacterial growth by most patients. However, this is not only a disturbing symptom to patients, but there is also a strong psychological association and the most common treatment administered to patients is lancing of lesions and systemic antibiotic therapy [1]. Lancing has been shown to be ineffective in HS and it has been noticed that the spontaneous duration of each flare is similar to that of a conventional course of oral penicillin. Nevertheless, the role of antibiotics is unclear. Although the HS lesions are most often found to be sterile, susceptible bacteria are occasionally found to aggravate the condition [10,11]. The role of the endogenous follicular flora is unknown and may represent an immunogenic factor different from that of a simple bacterial infection. Topical clindamycin has been found to be superior to placebo in the randomised, controlled trial by Clemmensen [12] in the treatment of HS. Similarly, Jemec and Wendelboe [4] did not find any difference between systemic tetracycline and topical clindamycin in another randomised, controlled trial. Whether the effect of these antibiotics is primarily due to a regular bacteriostatic action, or due to influences on the inflammatory response to HS, remains open to speculation.

Histologically, HS is a follicular disease with elements of occlusion and analogies have therefore been made to acne. In addition, the antibiotics tested in the two randomised, controlled trials are routinely employed in acne therapy. It is well-established that acne vulgaris can be treated with antiandrogens in female patients. In a similar manner, hormonal therapy has been attempted in HS and found to be effective. It has, however, been suggested that antiandrogen therapy was mainly effective in patients who also suffered from acne and cases have been published in which the onset of HS coincided with the use of oral contraceptives [13,14]. Furthermore, a randomised, controlled trial has been carried out to study whether the addition of cyproterone acetate would be of additional benefit over oestrogen therapy. In the treatment of HS, there was no significant difference between either therapy, which may be interpreted to suggest that the role of androgens is in fact less than expected. Similarly, finasteride has not been highly effective in the treatment of HS [15]. The efficacy of combined antihormonal therapies as well as hormonal and antibiotic therapies, have been reported in single cases, but even though HS may be seen in some patients as a marker of hyperandrogenism, it is not common [16,17]. The association between hyperandrogenism and HS is less well-established than the association to, for example, hirsutism or acne.

The analogy of acne has strong appeal and therefore, isotretinoin has also been tested in HS. The results are at best equivocal compared to the results in acne treatment. In acne, isotretinoin consistently shows the highest clearance rate of established systemic treatments, whereas only a small number of HS patients appear to benefit from the treatment [18]. Therefore the overall impression of this drug is that it is much less effective in HS than in acne [19,20]. Furthermore, it would

appear that the lax distinction between, for example acne conglobata and HS, has led to the inclusion of in-homogenous patient groups in several publications, making the effect of any given drug in HS more difficult to ascertain. Patients with acne conglobata frequently have lesions in inverse areas and generally respond well to isotretinoin, whereas patient with HS rarely have lesions in convex areas and appear to respond poorly. Related to the use of isotretinoin, etretinate and acitretin have also been used in the treatment of HS and cases describing the benefits of these treatments have been published, implying that these drugs may be superior to isotretinoin in HS [21,22]. Again no randomised, controlled trials are available to assess these claims in a more scientific fashion.

The limited systematic efforts at investigating medical HS therapy have been heavily influenced by previous acne therapy. The association between acne and HS is, however, restricted and the results have been correspondingly disappointing. The development of new therapies has therefore moved to related drugs or different concepts of disease pathogenesis.

Early studies have suggested that immunosuppressive therapy may be of benefit to these patients. Immunosuppression would alleviate problems due to inflammation, and simple immunosuppression would appear to be a therapeutic alternative in a similar way to many other inflammatory skin diseases. Intralesional steroids are an important clinically proven management tool for HS, although unsupported by formal studies. Systemic corticosteroids are also useful, although formal studies are also lacking here. Cases have been presented showing the beneficial effects of cyclosporin or dapsone to the management of HS [23,24]. No long-term results are reported, nor have larger case series been reported. In practical terms, anti-inflammatory treatment may also be seen as an intermediate form of therapy aimed at alleviating immediate symptoms and at preparing the patient for subsequent radical surgery. Similarly, pain management is an important adjuvant therapy to help patient overcome flares of the disease.

Changing the perspective on the disease to an inflammatory pathogenesis has been supported by a number of observations suggesting that there is a co-occurrence of HS and Crohn's disease. This has led to the pursuit of using treatments normally used for Crohn's disease in HS. Corticosteroids have been studied, as described above, but methotrexate has also been tested in a small open series [25]. The results, however, only suggested a weak effect on severity and no effect on recurrence rate.

Stronger immunosuppression appears to have a superior effect as shown by the cases describing the effects of infliximab or etanercept on HS [26-28]. These drugs either work by destroying (infliximab) or decoying (etanercept) the

pro-inflammatory cytokine, TNF- α , and are used in a growing number of other inflammatory diseases, such as Crohn's disease, rheumatoid arthritis and psoriasis. The initial cases appear highly promising, although the questions of potential side effects and long-term use have not yet been settled. Whereas this therapy may be appropriate for severe cases of HS, legitimate questions need to be answered regarding the costs and possible side effects involved in using this apparently promising new therapy for patients suffering from more limited disease.

4. Other factors

The prevalence of HS is comparable to other major dermatoses and has been found to occur in ~ 2% of the general population [1]. The efficiency of the current best practice (i.e., topical clindamycin, systemic tetracycline or hormonal therapy) is insufficient to provide relief to this large group of patient even if it were made available. The majority of patients has therefore lost confidence in the medical services and suffer in silence. In recent years, some degree of self-empowerment has appeared in several countries in the form of active patient associations [101]. These associations pursue venues for self-help and development. An increased patient awareness has therefore appeared, possibly facilitated by recent advances of the internet which allows interpersonal contact and discussion of this otherwise very private disease.

5. Expert opinion

HS is a common disease, causing considerable morbidity in patients. It affects private areas of the body, most patients prefer not to show and it affects them in a painful and for many, embarrassing way. Research into its causes has been hampered by direct interpretations of the symptoms which are analogous to other known diseases, the fact that many different specialities see these patients and finally, by the very private nature of this disease. Additional pathogenic research is therefore needed in order to tailor treatments more appropriate to significant pathogenic steps.

The disease can be treated surgically, but as it is a multifocal disease, medical treatment would hold many advantages. According to patient interviews, the current best practice is rarely carried out and even when it is, it is insufficiently effective in order to alleviate the suffering of most of the patients. The introduction of infliximab or similar drugs, for the treatment of HS holds some promise but the drug is unlikely to be widely available and therefore there is still a strong need for the development of new treatments for HS.

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