UPDATE ON ETIOPATHOGENESIS, RISK FACTORS AND TREATMENT OF HIDRADENITIS SUPPURATIVA

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Summary

Abstract: *The prevalence of hidradenitis suppurativa (HS) in general population ranges from 1% to 4%, while its etiopathogenesis is still incompletely determined and multifactorial. The management of these diseases is complex, as the current therapy does not a curative role but rather aims at reducing the chronic inflammation and maintaining the remission state, by preventing the worsening and progression of the disease.*

Objectives: *This paper is intended to summarize the updated data on HS etiology, the main risk factors involved, and the therapies used to manage this disorder.*

Material and method: *Based on the review of the specialty literature published during a time range of 8 years (2010-2017), we highlighted the news regarding the involvement of the internal and external factors in the onset of HS, and summarized the main therapeutic lines recommended by the new international therapeutic guidelines.*

Results and discussions: *The main factors involved in the development of HS are genetic predisposition, immunity and hormonal effects. The additional factors that maintain and cause worsening of the chronic inflammation are bacterial infections, smoking, obesity and mechanical friction.*

In terms of therapeutic options used in HS, we must mention the major role of antibiotic, corticosteroid or retinoid therapies in keeping the inflammation under control and mitigating the immune response. The use of biologicals, mainly anti-TNFα agents, has had encouraging results, improving the quality of life of these patients. In severe stages, when patients have extended lesions, the surgical excision is considered the only curing method. Dapsone therapy has good results, but the adverse events are multiple. Cryotherapy, CO_2 laser therapy, PDT or low-dose radiotherapy continue to be complementary methods associated with modest results and frequent relapses.

Conclusions: *Patients with genetic predisposition or with specific immunity have a higher risk of developing HS when other external factors such as smoking and obesity are associated. HS treatment should be customized and should consist of medical therapies, surgical regimens and the use of complementary methods, and it is often necessary to combine these to control the disease.*

Key words*: hidradenitis suppurativa, etiopathogenesis, risk factors, medical treatment, surgical excisions, complementary methods.*

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Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent inflammatory condition of the follicular epithelium, characterized by pimple-like bumps follicular occlusions with recurrent abscess formation, sinuous pathways and progressive scarring, which primarily affects the flexural areas of the body affluent in apocrine glands.

This condition is also known as Verneuil's disease (historical name), named after the French surgeon who, in the 19th century. related the clinical manifestations of HS to the clinical signs

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and symptoms of a conditions of apocrine glands [1]. Subsequently, the pathogenesis related to the follicular oclusion. The follicular triad includes HS along with dissecting cellulitis of the scalp (*perifolliculitis capitis*) and acne conglobata, while the follicular tetrad also adds pilonidal cyst to this classification. At the beginning of the 90's, the term inverted acne (*acne inversa*) was proposed as an alternative, while the apocrinitis term is used especially in English literature.

Currently, some authors consider that none of the current names is accurate enough for this pathology if we were to consider the multifactor pathology and the mechanisms involved in the development of HS.

The disease onset could occur after puberty, during the second decade of life, and it is more common in women (F:M=3:1)[2]; however, it has a more severe and refractive progress in men, sometimes under standard therapy.

HS is an increasingly common condition, has doubled in prevalence throughout time, from 4.3 cases / 100,000 inhabitants during the 1970-1979, to 9.6 cases /100,000 inhabitants during 2000-2008 [3].

Objectives

This paper aims at summarizing the updated data on the etiopathogenesis and risk factors involved in the development of HS and at reviewing all therapeutic options (including medical, surgical, or complementary treatments) used to treat this condition, focusing on studies of efficacy, tolerability, possible therapeutic associations, and the safety of their use and limitations.

Material and method

We have reviewed 13 clinical trials and 8 reviews, but also the recommended European Guideline on HS, published in the specialty literature during 8 years (2010-2017), and we used search engines such as Pubmed, Medscape, Wiley online library, Springer , ResearchGate and Science by directly entering keywords such as: „the etiology of hidradenitis suppurativa", „risk factors", „treatment guideline in HS", „biological therapies and HS" We highlighted the news regarding etiology and the involvement of risk factors in the onset of HS, and we summarized the main therapeutic lines recommended by the new international therapeutic guidelines.

Results and discussions

Although HS is an intensely debated pathology among researchers and clinicians, the management of this condition is not yet standardized, and the choice of optimal treatment depends on the severity of the disease, the associated risk factors, the patient's compliance and adherence to the treatment, the availability of an interdisciplinary team and the legislation in force.

Following the analysis of the studies mentioned in this article, we have summarized the most important data regarding the diagnosis and treatment of this condition.

The etiopathogenesis of this condition continues to be a partial mystery, however, it was agreed that follicular hyperkeratosis is the starting point that induces infundibular obstruction. This phenomenon is secondarily accompanied by dilation of the pilosebaceous unit followed by follicular rupture with extravasation of the content into the dermis and the triggering of a local inflammatory response that stimulates the proliferation of pro cytokines and anti-inflammatory agents, thus perpetuating the process.

Considering the latest information on the etiopathogenesis of this condition, mainly the data on immunity and inflammation, we highlight that the theory placing the infundibular obstruction as the main event in HS, agreed by several authors, is not unanimously accepted. Abnormal activity of the innate and acquired **immune response** in these patients has raised many hypotheses. While some researchers have observed inhibition of toll-like receptors 2,3,4,7 (markers of innate immunity) by dendritic cells in HS lesions, others have demonstrated their overexpression [4] [5]. At the same time, there are contradictions regarding the involvement of antimicrobial peptides such as beta-defensin 2, psoriasin or cathelicidin, expressing both their overexpression and inhibition [4][6]. All these facts provide actual evidence of idiosyncratic heterogeneity in the affected individuals, and the differences in the expression of these markers

could be related to the different stages of the disease.

A recent article [7] even suggests that HS may be among the auto-inflammatory disorders characterized by recurrent inflammatory episodes in the absence of infection and by the presence of specific antibodies or antigens. In HS lesions, increased levels of proinflammatory cytokines such as TNFα and IL1β (cytokines involved in most auto-inflammatory diseases) have been determined, and these increases correlate with the severity of the disease [1]. Macrophages, T-lymphocytes, and mast cells found in lesions also cause elevated levels of anti-inflammatory cytokines, including IL-10, which yields a negative feedback to the pro-inflammatory cascade. Schlapbach et al. has brought into attention the fact that increased levels of IL-12 and IL-23 in the papillary and reticular dermis of HS lesions suggest an active IL-23 / Th17 pathway, the potential target of monoclonal antibodies such as Ustekinumab [8].

The triggering and sustenance of this inflammatory chronic process is also favored by patients' genetic background, hormonal factors, bacterial infections, and external factors such as smoking and obesity.

Regarding the **genetic factor,** it is considered that about 40% of first degree relatives of HS patients also develop this disease [10], the reports showing an autosomal dominant transmission with incomplete penetrance [11]. Several HS susceptibility loci associated with HS have been identified to date, including 1p21.1-1q25.3 [9]. Mutations of PSENEN, PSEN1 and NCSTN genes (these encode proteins belonging to the proteolytic Gamma-secretase complex) have been identified in families with HS history [13] [14]. Studies in mice have shown that impaired activity of gamma secretase leads to follicular keratinization, atrophy, epidermal cyst formation and epidermal hyperplasia, characteristics that can also be found in the HS [12].

Predominance in female subjects, pre-menstrual exacerbations, post-pubertal onset as well as improvement of lesions during pregnancy have drawn attention over the involvement of the **hormonal factor** in HS pathogenesis. The hypothesis of hyperandrogenism was not supported in the absence of clinical signs of virilism, hyperseborrhea, by the presence of normal levels of circulating androgenic hormones, and the limited effect of antian-drogenic treatments. It is believed that elevated levels of free androgens are the result of low levels of sex hormone binding globulin correlated with body weight [13].

It has been considered for a long time that bacteria play an essential role in the occurrence of HS. However, cultures isolated from lesions have often been sterile or have revealed the presence of a commensal flora: staphylococci, streptococci, E. coli, etc.; thus, the **microbial factor** is not currently considered a causal factor, but might play an important role in clinical manifestations [16]. This theory is supported by a study showing that the cultures were negative in 51% of the cases [17], suggesting that HS is a disease primarily affecting the follicular epithelium, and bacterial colonization appears as a secondary event.

Smoking is an important risk factor, often associated with HS (77-88.9% of patients are smokers) [18]. Nicotine and polyaromatic hydrocarbons are two of the hundreds of components that go into the composition of a cigarette. They activate keratinocytes, fibroblasts and act on nicotinic acetylcholine receptors and aryl hydrocarbon receptors [19]. By activation of proinflammatory cytokines such as TNFα, IL 1α, 1β and IL8 [19], alterations of neutrophil chemotaxis and T helper17 lymphocytes occur (induction role in the adaptive immune system through cytokine secretion). Although it is not yet clear whether smoking cessation could improve the course of this disease, however, a case study [20] was reported in which 2 patients experienced a complete remission of the disease after giving up smoking.

Obesity is another triggering factor involved in HS pathogenesis. In 55% to 80% of cases, these patients have a body mass index over 25 kg / m^2 (BMI> 25) [21]. In addition, it was observed that individuals with a BMI > 30 kg / m^2 develop more severe clinical manifestations than individuals with normal weight [22]. Obese people have increased levels of proinflammatory cytokines: TNFα, IL1β, and IL6. These increased levels of cytokines, especially TNFα and IL1β, are also found in HS lesions; therefore, this chronic proinflammatory status of chronic partial and

adipocyte production could contribute to the onset and development of HS.

Other factors: Antiperspirants and chemical irritation could trigger or exacerbate HS as they cause pore clogging and alteration of axillary commensal flora. Also, the use of shaving devices can increase the risk of disease development, as infundibular transection favors bacteria access at this level [23]. A retrospective study of 45 patients showed that 10 of these patients had a personal history of mechanical irritation before the onset of the disease; the causes were various, ranging from shaving devices use to mechanical friction due to prosthetic wear [23].

HS diagnosis is a clinical one based on the following criteria: insidious onset with painful subcutaneous nodules, abscesses, sinuous pathways, fistulas, scars; they affect predominantly the folding areas of the skin rich in apocrine glands; tendency towards chronicization and frequent recurrences. The most frequently affected areas are the armpits, the anogenital area, the buttocks, the perineum area, the infra- and inter-breast folds.

In order to assess the severity of the disease, the Hurley clinical staging system was introduced in 1989, based on the presence and severity of fistulas and scarring [16] [24] as follows: Stage I - single / multiple, recurrent abscesses, without sinuous pathways, fistula or fibrous scarring processes; Stage II - single / multiple recurrent abscesses, with the presence of fistulas, sinuous pathways and scars, separated by normal appearance skin; Stage III - diffuse extent, with abscesses and sinuous interconnected pathways, without interference of normal skin.

HS treatment often requires a multidisciplinary team capable of providing adequate medical and surgical treatment.

Diet, weight control, smoking cessation, and avoiding trigger factors along with medical therapies or surgical regimens are essential in HS management.

The medical groups used in HS treatment comprise antibiotics, hormonal treatments, immunosuppressant agents (corticosteroids, cyclosporine, anti-TNFα and IL-inhibitors, etc.). Acitretin and even low-dose isotretionin can be used in the early stages, in combination with other therapies.

Antibiotic therapy, through its anti-inflammatory properties and its ability to act on microbial biofilm, is the most effective conventional therapy, being the most commonly prescribed by treating physicians [25]. In a retrospective study conducted by Mendonca and Griffiths in 2006 that included 14 patients who had treatment with Clindamycin (300 mg) and Rifamipicin (300 mg) twice a day for 10 weeks, the following results were obtained: 57% of them had a complete remission of lesions, while 28% withdrew from treatment due to adverse effects [17] [26].

Another study conducted on 116 patients with the same treatment confirmed the efficacy of Clindamycin associated with Rifampicin over a 10-week period. The results were evaluated using the Sartorius severity score, whose median decreased considerably from 29 to 14.5 ($P < 0.01$) after treatment [17] [26] [27]. Regarding the effectiveness of local topical antibiotics, the effect of topical 0.1% Clindamycin compared to placebo in a group of 27 patients [17] showed a favorable effect after 3 months of topical treatment, with the reduction of abscesses, inflammatory nodules and pustules.

A randomized trial conducted on a batch of 46 patients compared the effectiveness of 0.1% Clindamycin applied topically twice daily versus oral Tetracycline 1 g / day. At the end of the 3 months of treatment, statistically significant differences were not reported, proving that oral medication is not superior to the topical medication [17].

Other antibiotics used in the treatment of HS are Doxycycline, Clarithromycin, Minocycline, Rifampicin in combination with Moxifloxacin or Metronidazole, with variable results.

Another study led by Join-Lambert et al. [28] with 28 patients enrolled revealed that 57% of them had a complete remission of the disease after treatment with Rifampicin in combination with Minocycline or Metronidazole. The results could have been influenced by the fact that, prior to initiating this therapy, patients received Ceftriaxone injection for 2 weeks as induction therapy.

At the same time, the combination of Amoxicillin and Clavulanic Acid can be extremely effective if administered within the first hour after symptom onset [16].

Retinoids: Despite current medical evidence showing limited efficacy of Isotretinoin in the treatment of HS, it remains a commonly prescribed therapy by dermatologists. Of the 64 patients included in a study, only 23% reported the remission of lesions after a 4-6 month treatment period, 29% of them discontinuing therapy due to its ineffectiveness or the development of adverse effects [17] [25]. 30% of all patients who had reached flare-up relief have experienced relapses during the follow-up period.

During the past few years, a slight increase in Retinoid efficacy has been reported in narrow trials.

In a 2014 prospective study [29], 14 patients with known moderate / severe HS were treated exclusively with Acitretin 0.5 mg / kg, achieving a good response in 53% of the cases. Although the initial results were encouraging, all patients relapsed within the next 8 months after the completion of therapy. Puri and Talwar [30] compared the efficacy of Acitretin used alone versus Acitretin combined with surgical treatment (surgical excisions), reporting a much lower rate of recurrence and a 20% rate of recurrence respectively for therapeutic association compared with Acitretin monotherapy where the relapse rate was 40%.

Small doses of Alitretinoin (10 mg / day) have been shown to be effective in a group of 14 women. A significant improvement of the disease was seen in these patients, suggesting that Alitretinoin could be a good alternative to Acitretin in women of childbearing age [31].

Corticosteroids. Administration of high-dose systemic corticosteroids ensures good control of the progressive flare-up by reducing inflammation and pain, but the dose reduction quickly leads to recurrences. An alternative that would reduce the risk of adverse effects is the administration of low doses for longer periods of time. Intralesional injection of steroids (e.g. Triamcinolone acetonide) enables remission to be reached within the first 12-24h.

Contrary to the proven efficacy of **Cyclosporine** in the treatment of psoriasis, by direct action on T lymphocytes, IL2 and TNFα, isolated HS cases have been reported that have responded favorably to this therapy. **Methotrexate** ineffectiveness in HS has been determined based on 3 clinical cases treated with this medicine [23]. Other immunosuppressive therapies such as Azathioprine or Mycophenolate mofetil could be effective in treating HS, but there are no studies to confirm their efficacy.

The efficacy of **hormone therapy** was assessed by performing a crossover study on 24 women with HS divided into 2 groups, the first group receiving treatment with Cyproterone acetate and Ethinylestradiol, and the 2nd group treated with Ethinylestradiol and low doses of Norgestrel. Seven of these patients (29%) achieved complete and lasting healing, with no proven statistical difference between the two treatments [25]. Although hormone treatment could improve disease progression in some cases, the low success percentage reveals the limited action of this therapy in HS.

In 2013, Radhawa et al. [33] have investigated the benefits of **5-alpha reductase inhibitors** in children and adolescents with HS. Finasteride, in combination with oral contraceptives or systemic antibiotics, led to relief of lesions and reduced inflammatory recurrences in the 3 patients included in the study, which is why the authors suggested its possible use as an additional therapy in cases of female patients or pediatric cases with HS refractory to treatment.

The introduction of **biological therapies** in HS management has provided an optimistic non-surgical approach, particularly in patients with severe disease and disease refractory to conventional treatments. TNF-α is a pleiotropic proinflammatory cytokine, whose stimulation induces the activation of a cascade of inflammatory reactions that cause excessive inflammation. The inhibition of the tumor necrosis factor plays an important role in treating several inflammatory diseases, including HS. Recently published results have revealed the favorable effects of anti-TNFα therapies in the treatment of this disease [35] [36] [37] [38] [39].

Infliximab (IFX) is the first biological agent to have shown effectiveness in HS patients and associated Crohn's disease. In a randomized placebo-controlled trial, Grant et al. analyzed the effectiveness of Infliximab on a group of 38 patients enrolled. 26% of patients treated with INN had a reduction in the severity of the disease by more than 50% compared to the placebo arm

(5%). [39] The results of this study confirm the efficacy of this anti-TNFα agent which reduces activity disease, by decreasing pain and inflammation and significantly improving the quality of life of patients. Despite the encouraging results, recurrences occur at varying intervals. While it has long been considered that **Etanercept** treatment has similar effects to Infliximab [24], recent data suggest that there are no significant differences between patients treated with Etanercept and those treated with placebo (results obtained after the patient's overall assessment and DLQI) [40].

Adalimumab (ADA) 40 mg given subcutaneously on a weekly basis or every 2 weeks is the most studied biological agent with dose-dependent results; thus, in a randomized, double-blind, placebo-controlled trial [36] including 154 adults with moderate / severe HS, the benefits of ADA were assessed; the findings showed that after week 16 (S16) of therapy, clinical response was obtained from 17.6% of patients treated weekly versus 3.9% of placebo-treated patients.

In patients treated with ADA every 2 weeks, the clinical response was reached in 9.6% of cases.

Recently, treatment with **Ustekinumab (UST)**, a monoclonal antibody that acts on the P40 subunit of IL12 and IL23, was also assessed. Data on this biological agent are scarce, 6 cases [41][42][43][44] treated with UST and a clinical trial involving 17 patients [45] have been reported in the literature. The results of this study showed that 47% of the 12 patients who completed the therapeutic protocol achieved significant clinical improvements at Week 40. One should note that the therapeutic response was not quick, with clinical improvements becoming noticeable after a few months after the initiation of treatment.

Data on the effectiveness of other biological agents such as **Ankinra** or **Canakinumab** are very scarce [24] and require detailed studies to evaluate their efficacy and tolerability.

Currently available medical methods control the flare-up progress and reduce inflammation, but their efficacy is often transient. Therefore, in patients with severe, extensive lesions, surgical removal of the tissues involved is necessary.

Surgical treatment varies depending on the severity of the disease, but also on the location of the lesions (risk of scarring contractions). Thus, in the incipient stages, the incision and drainage of the lesions are the preferred methods, while for the moderate stages with limited lesions and recurrent abscesses, the local excision with per primam suture can be performed. In the severe stages with diffuse extent, the best option is radical, wide and deep excision, followed by reconstructive skin grafts or flaps [24]. Rompel and Petres [46] [48] have followed up the long-term evolution of 106 patients who had undertaken radical excision and the results obtained after 36 months showed a recurrence rate of only 2.5% on the surgical areas, and wound infection in 3.7% of these patients.

The success rate of radical excisional cures was evaluated in a retrospective study [50] of 106 patients, in which: 100 injuries were selected for local excision with per-primam sutures, 29 of the lesions were subject to radical excision followed by skin grafting, and 14 lesions were subject to radical excisions followed by reconstructions with fascio- or musculocutaneous flaps. Recurrences in the case of per primam sutures were reported in 69.9% patients, whereas in the case of excisions followed by reconstructions or skin grafts, relapses were not reported. Another retrospective study [51] in which 31 patients underwent procedures for drainage of abscesses, limited local surgery or broad radical excisions confirmed the therapeutic benefit of radical surgeries, indicating a relapse rate of only 27% at 72 months, compared with 42.8% for limited excisions or 100% for drainage. In conclusion, surgical treatment continues to be an effective method, which ensures long-term control of the disease and considerably decreases the rate of relapses.

CO_2 Laser: Lapins el al. have studied the efficacy of CO_2 laser therapy on 24 patients with HS, the results obtained after a 27-month follow-up period being some of the most advantageous, with only 2 patients presenting relapses. Another study [53] conducted by Lapins in 2012 revealed that, although this therapy offers good results with a minimal number of recurrences in the treated areas, however, remote relapses are common.

Hazen and Hazen [54] treated a batch of 61 patients, 185 lesions, with CO_2 laser combined with a marsupialization technique, reaching

complete healing of 183 of the 185 lesions without recurrence during the follow-up period ranging between 1 and 19 years of age.

The use of **photodynamic therapy (PDT)** has been derived from its effectiveness in the treatment of acne vulgaris by reducing sebum production. The mechanism of action involves the absorption of aminolevulinic acid, followed by an increase in protoporphyrin IX production in hair follicles. In the case of HS, the results are controversial, with a lesion improvement rate of 0% to 100%. The **Nd-YAG 1064nm laser** is a complementary method in the treatment of HS. The effectiveness of this therapy consists in triggering a selective photothermolysis of the pilo-sebaceous unit. Tierrrey et al [55] studied the effects of the Nd-YAG laser on a group of 22 patients with HS in Hurley II and III stages; a significant decrease in the severity of the disease within 3 months was reported (65.3%).

In cases where systemic therapy is contraindicated and the patient refuses surgery, Pagliarello et al. [56] have proposed a new technique, i.e., **cryotherapy**. This technique involves the injection of liquid nitrogen directly into sinuous pathways. As the liquid nitrogen enters the infected sinuses, it quickly disperses into the communicating pathways due to the high expansion coefficient of the liquid in the gas. This is a new, easy-to-use, inexpensive therapy that can be used alone or as adjunctive therapy with rapid results and significant clinical improvements.

Although it has been widely used in the past, showing good results, **radiation therapy** is currently no longer used due to the increased risk of neoplasia in the gluteal or intergluteal region.

Only one case [57] of HS treated with **botulinum toxin** was published. 250 botulinum toxin units were used in one session, and the inflammatory lesions were completely remitted within the next 10 months. The principle of effectiveness is that botulinum toxin reduces the secretion of apocrine glands and limits follicular rupture.

Other complementary methods include zinc gluconate, resorcinol peeling and Dapsone.

Zinc gluconate at doses of 90 mg / day administered over a 12-month period had a favorable progression in a group of 22 patients [58], with complete remission of 8 patients (36.3%) and improvement of the other 14 patients. The adverse effects experienced by patients included nausea and macrocytic anemia. [58] The efficacy of this therapy results from the anti-inflammatory and antiandrogenic properties of 5-a reductase-inhibiting zinc gluconate.

After long-term treatment with **Dapsone** (2 years in average), significant clinical improvements were observed for doses of 50-200 mg / day, with an improvement of 38% of the total of 24 patients included in the study [46] [59]. The efficacy of Dapsone derives from its antibacterial and anti-inflammatory properties, particularly due to its inhibitory effect on neutrophil chemotaxis. However, this therapy should be used with caution due to its adverse effects.

Topical resorcinol 15% has shown a mild efficacy in relieving pain and reducing inflammation in patients with HSH- Hurley stage I / II [46] [59], but further studies are needed to draw valid conclusions regarding the efficacy and tolerability of this therapy.

So far, there is no consensus on the optimal treatment of HS, but European treatment Guidelines for HS [59] have been published to address the management of the condition according to Hurley clinical staging. This must be often customized individually and consists of medical therapies, surgical regimens and the use of complementary methods, and it is often necessary to combine them to control the disease.

Conclusions

HS is a chronic, debilitating disease that requires a complex combination of medical and surgical treatments. The care of these patients should be managed by a multi-disciplinary team (dermatologists and surgeons alike) appropriately trained to provide these patients with optimized individualized treatment tailored to the degree of severity of the disease but also to the patient's wishes. HS treatment aims at reducing chronic inflammation and follicular occlusion, relieve pain, flare-up healing, and maintain remission by preventing worsening and progression to more severe stages, and last but not least, improving the quality of life of these patients.

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Conflict of interest
NONE DECLARED

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