Avanços na Hidradenite Supurativa: Da Etiopatogenia ao Tratamento

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RESUMO – A hidradenite supurativa é uma dermatose inflamatória crónica, recorrente, do folículo piloso. A prevalência de hidradenite supurativa é debatida, com taxas estimadas tão baixas como 0,00033% e tão altas como 4,1%. A prevalência da hidradenite supurativa parece ser significativamente maior nas mulheres. A sua etiopatogenia parece envolver hiperqueratose folicular com obstrução, dilatação e consequente rutura do folículo piloso, resultando em inflamação e formação subsequente de abcessos e trajetos sinuosos. A etiologia é provavelmente multifatorial, envolvendo fatores genéticos, tabagismo, *stress* mecânico, obesidade, resposta aberrante imune e anormalidades hormonais. A hidradenite supurativa, como dermatose inflamatória crónica, está associada a uma variedade de doenças concomitantes e secundárias, como síndrome metabólica, doenças inflamatórias e reumatológicas, depressão e neoplasias. Assim a abordagem da hidradenite supurativa requer uma equipa multidisciplinar.
PALAVRAS-CHAVE – Hidradenite Supurativa/diagnóstico; Hidradenite Supurativa/patologia; Hidradenite Supurativa/tratamento.

Update on Hidradenitis Suppurativa: From Etiopathogenesis to Management

ABSTRACT – *Hidradenitis suppurativa is a chronic, inflammatory and recurrent skin disease of the hair follicle. Prevalence is a matter of debate, with estimated rates as low as 0.00033% up to 4.1%. Hidradenitis suppurativa prevalence appears significantly higher in women with a mean age of onset in the early 20s. The primary histopathologic event seems to be a follicular hyperkeratosis with plugging, dilation and rupture of the hair follicle resulting in subsequent inflammation and formation of abscesses and sinus tracts. The cause is likely multifactorial, involving genetic factors, cigarette smoking, mechanical stress, obesity, immune aberrant response and hormonal abnormalities. As a chronic inflammatory dermatosis, hidradenitis suppurativa is associated with a variety of concomitant and secondary diseases such as metabolic syndrome, inflammatory and rheumatologic diseases, depression and malignancy, and, therefore, management often requires a multidisciplinary team.*
KEYWORDS – *Hidradenitis Suppurativa/diagnosis; Hidradenitis Suppurativa/therapy; Hidradenitis Suppurativa/pathology.*

INTRODUCTION

Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil´s disease, is a chronic, inflammatory and recurrent skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body.[1] Originally described by Verneuil, in 1854, the pathogenesis was attributed to a disorder of the apocrine sweat glands, hence the name "hidradenitis".[2] The perception that the main event in the origin of HS involves the hair follicle as in acne-like disorders lead to the suggestion of the term acne inversa.[3]

More studies on epidemiology and pathophysiology are

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currently underway, and seem mandatory to better understand this disease and improve therapeutic approach.

1. DEFINITION AND DIAGNOSIS

The diagnosis of HS is clinical. According to the modified Dessau definition, 3 criteria must be present: typical lesions, including nodules, sinus tracts, abscesses, scarring and double-ended pseudocomedones; location in at least one area for which HS has a predilection namely the axilla, genitofemoral area, perineum, gluteal area and infra- and intermammary folds (although lesions may appear ectopically); and history of chronicity and recurrence (more than 2 recurrences over a period of 6 months).[1,4]

2. DIFFERENTIAL DIAGNOSIS

Several infectious and non-infectious dermatoses need to be differentiated from HS (Table 1).

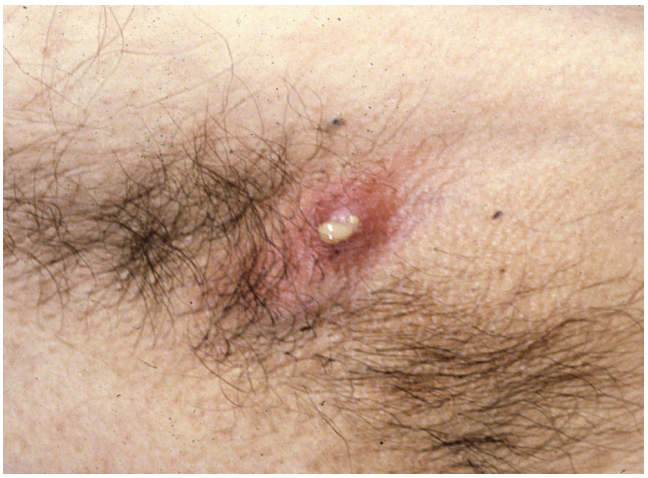

Figure 1 - Typical case of HS patient with Hurley 1 disease.

Table 1 - Differential diagnosis of hidradenitis suppurativa*.

Carbuncle	Cutaneous Crohn disease	Noduloulcerative syphilis
Epidermoid/dermoid cyst	Simple abscesses	Blastomycosis
Erysipelas	Neoplasms	Scrofuloderma (Tuberculosis)
Furuncle	Lymphogranuloma *venereum*	Granuloma Inguinale/Donovanosis
Pilonidal cyst	Cutaneous actinomycosis	

*Adapted from Zouboulis *et al*.[1]

3. CLASSIFICATION AND SEVERITY ASSESSMENT

3.1 - Hurley staging

In 1989, Hurley[5] first proposed a severity classification consisting in 3 stages (Table 2). Stage I disease is the most common (68% of patients), while stage II occurs in 28% of patients, and 4% of HS patients have stage III.[1] Hurley classification is useful for quick HS severity assessment. However, it is not a precise monitoring tool, namely for accessing therapeutic efficacy.[1,4] Fig.s 1, 2 and 3 illustrate typical cases of HS patients with Hurley 1 to 3 disease, respectively. Recently, a revised version of Hurley staging was proposed.[6] It consists on a 3 steps algorithm, including assessing the

Table 2 - Hurley staging*.

Stage I - Abscess formation, single or multiple, without sinus tracts and cicatrization
Stage II - Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions
Stage III - Diffuse or near-diffuse involvement or multiple interconnected tracts and abscesses across the entire area.

*Adapted from Hurley.[6]

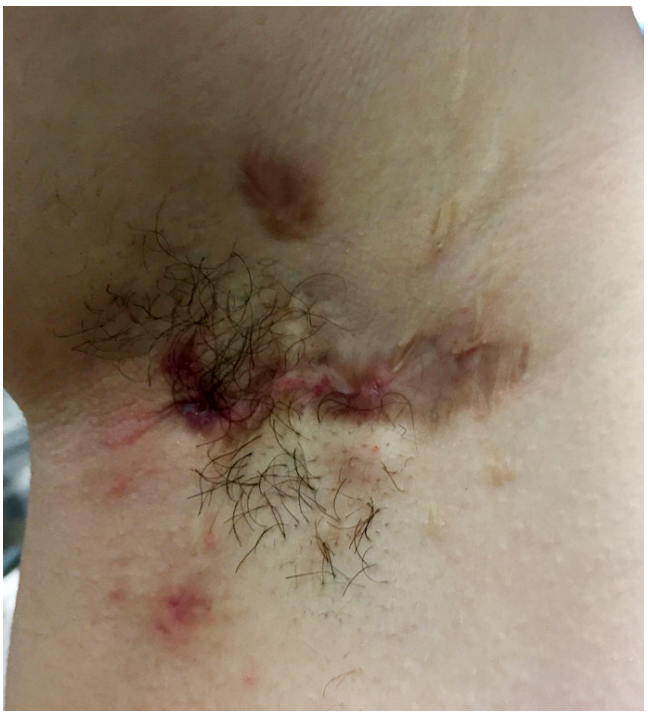

Figure 2 - Typical case of HS patient with Hurley 2 disease.

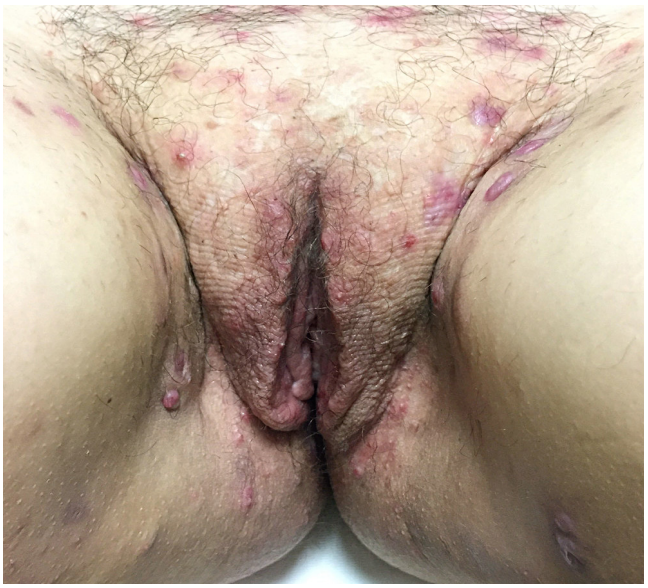

Figure 3 - Typical case of HS patient with Hurley 3 disease.

presence of sinus tracts, degree of inflammation and the extension, which enables the clinician to assess severity across the different phenotypes of HS and helps guiding treatment.[6]

3.2 - Sartorius Score

This scoring system, described in Table 3, was the first disease specific instrument for dynamically measuring clinical severity.[1] The parameters in the modified Sartorius score include counting of individual nodules and fistulas, measuring the longest distance between 2 lesions, and adding extra points to Hurley III stages.[7] It is rarely used in clinical practice as it is time consuming and complex.

Table 3 - Sartorius Score*.

I- Anatomical region involved (axilla, groin, gluteal or other region or inframammary region left and/or right: 3 points per region involved).
II- Number and scores of lesions (abscesses, nodules, fistulas, scars: points per lesion of all regions involved: nodules 2; fistulas 4; scars 1; others 1).
III- The longest distance between two relevant lesions, i.e. nodules and fistulas, in each region, or size if only one lesion (< 5 cm, 2; < 10 cm, 4; > 10 cm, 8).
IV- Are all lesions clearly separated by normal skin? In each region (yes 0 / no 6).

*Adapted from Sartorius *et al*.[7]

3.3 - Physician Global Assessment (PGA)

Currently, PGA, a 6 stages classification, is the most frequently used tool in clinical trials to measure treatment efficacy (Table 4).[1,8]

Table 4 - Physician Global Assessment*.

Clear - No inflammatory or non-inflammatory nodules
Minimal - Only the presence of non-inflammatory nodules
Mild - <5 inflammatory nodules without abscesses and draining fistulas or 1 abscess or draining fistula without additional inflammatory nodules
Moderate - <5 inflammatory nodules, or 1 abscess or draining fistula and ≥1 inflammatory nodules, or 2-5 abscesses or draining fistulas and <10 inflammatory nodules
Severe - 2-5 abscesses or draining fistulas and ≥10 inflammatory nodules
Very severe - >5 abscesses or draining fistulas

*Adapted from Kimball *et al*.[8]

3.4 - Hidradenitis Suppurativa Clinical Response (HiSCR)

The HiSCR score is defined as a ≥ 50% reduction in the number of transient inflammatory lesions (sum of abscesses and inflammatory nodules) and no increase in abscesses or draining fistulas (chronic inflamed lesions) when compared with baseline.[9] However, it is designed to assess treatment response, not disease severity cross-sectionally.[4]

3.5 - International Hidradenitis Suppurativa Severity Score System (IHS4)

The novel IHS4, a systematically constructed, validated and simple tool to dynamically assess HS severity, can be adapted both to clinical research and daily practice.[10] IHS4 evaluation requires counting of nodules, abscesses and draining fistulas/sinus tracts (Table 5).

Table 5 - International Hidradenitis Suppurativa Severity Score System (IHS4)*.

Number of nodules **multiplied by 1**
Number of abscesses **multiplied by 2**
Number of draining tunnels (fistulae/sinuses) **multiplied by 4**
A score of ≤3 signifies mild HS; a score of 4-10 signifies moderate HS and a score of ≥11 signifies severe HS.

*Adapted from Zouboulis *et al*.[10]

3.6 - Medical imaging techniques

Staging and monitoring have been traditionally based on clinical findings.[11] However, HS is characterized by predominantly dermal pathology and therefore, difficult to assess clinically.[12] Physical examination has important limitations with poor sensitivity for differentiating lesion subtypes and defining disease activity.[11,12] Recently, noninvasive imaging techniques as ultrasound (US) and magnetic resonance

imaging (MRI) were shown useful and allowed a better understanding of HS as a pathology with subclinical anatomical manifestations undetected by clinical examination.[11-13] These imaging techniques can also be crucial to guide surgeons in the complete removal of chronic HS lesions, important in HS management.[11-13] Finally, these techniques may improve the diagnosis of Marjolin ulcers in HS, which is a rare but serious complication.[11,13,14]

Recently proposed US diagnostic and staging criteria are also important for a standardized HS nomenclature.[11,12,15]

4. PAIN ASSESSMENT IN HS

Pain in HS has many components namely nociceptive, neuropathic, inflammatory, ischemic and pain related to comorbidities.[16]

Reflecting its importance, many instruments have been created to assess therapeutic efficacy in drug trials. The numerical rating scale (NRS), where 0 denotes no pain and 10 severe pain, is a reliable tool for a baseline pain assessment.[16] Another instrument, the Visual Analogue Scale (VAS), although subjective, allows evaluation of pain severity in a continuous way (Fig. 4).

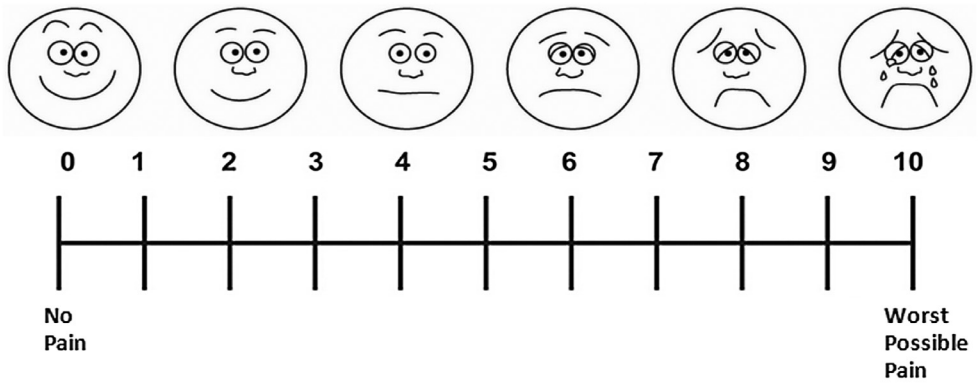

Figure 4 - Visual Analogue Pain Scale. Adapted from Yale University.[141]

5. PSYCHOSOCIAL IMPACT

As a chronic painful disease, HS is, not surprisingly, associated with poor quality of life (QoL).[1]

HS has a far-reaching effect on all areas of life and QoL has been found to be more significantly impaired in HS than in diseases like psoriasis, neoplasms, strokes or even heart transplant candidates.[17,18] Furthermore, problems in the familial and social environment, suicidal ideas, fear of stigmatization, and economic difficulties, contribute to the substantial burden of disease.[1] Some studies underline the significant work disability rate together with high unemployment rate among HS sufferers.[1,19,20] An additional contributor to impaired QoL is sexual dysfunction, particularly because of the influence of HS on intimate relationships and sexual activity.[18,21]

6. EPIDEMIOLOGY

HS is an under recognized entity with a significant delay from the onset of symptoms to the diagnosis,[22,23] with a median delay of 12 years in one study.[24] Prevalence is a matter of debate, with estimated rates as low as 0.00033% up to 4%.[18] A recent USA population-based study found an overall annual incidence of 6 per 100 000.[25] However, in Europe two studies reported a much higher prevalence of 1%[26,27] and Jemec *et al*[28] even found a prevalence of 4% in a young adult female population in Denmark. Discrepancies between European and American studies may be due to different methodologies.[1] Recently, a Portuguese nationwide hospital-based study showed a 15-year HS prevalence of 0.075%, but it included only patients who sought healthcare services, indicating that HS may be strongly underdiagnosed and mostly undertreated.[29]

HS is mainly a disease of young adults with no specific racial predilection.[30] The age of onset ranges from the second to the fifth decade, with a mean in the early 20s.[18] However, HS has also been reported in children and after menopause.[18,31,32] In fact, 2% of cases occur before the age of 11.[32]

HS prevalence appears to be significantly higher in women, with female: male ratios ranging from 2.5:1 to 4:1.[22] This ratio decreases in older patients as there is considerable evidence of a decline in prevalence in women after the age of 55 and not so evident in males, which may reflect hormonal changes due to menopause.[18,26]

7. PATHOGENESIS

The exact mechanisms underlying HS are not entirely established.[33] Due to its characteristic localization in regions with a high density of apocrine glands, it was initially assumed that the inflammation of these glands, the so called apocrinitis, was the primary event.[34] However, it is now generally accepted that apocrine glands are secondarily involved and the primary histopathologic event seems to be

follicular hyperkeratosis with plugging, followed by dilation and rupture of the hair follicle with subsequent inflammation and formation of abscesses and sinus tracts.[34] The cause is likely multifactorial, involving a genetic tendency, smoking, mechanical stress, obesity, immune aberrant response and hormonal abnormalities.[33]

7.1- Inflammation

HS is closely linked to other immune-mediated diseases and responds to immunosuppressive agents, suggesting, at least in part, an immune basis for this disease.[18]

Tumor necrosis factor alpha (TNF-α), although present in inflammatory HS skin, may not be the key player in its pathogenesis.[33] A recent study demonstrated enhanced mRNA expression of TNF-α in lesional and perilesional HS skin, but it was less pronounced than the increase of IL-17 and IL-1beta.[33,35] Furthermore, the proinflammatory cytokines IL-12 and IL-23 are abundantly expressed by macrophages infiltrating papillary and reticular dermis in HS.[36]

A subclinical inflammatory state occurs in the skin prior to the onset of a visibly active HS.[33] The process may begin as an aberrant keratinocyte response to bacteria of the normal microbiome with inappropriate production of cytokines and antimicrobial peptides.[37] Attracted immunocytes further secrete pro-inflammatory cytokines and chemokines.[38] Enhanced by obesity, smoking and defective Notch signaling, in the inflammatory microenvironment the follicular epithelium responds with hyperplasia, infundibular keratosis, follicular occlusion and cyst formation.[37,38] Cysts expand, rupture and expel contents into the dermis including bacteria and keratin, triggering a neutrophilic foreign body reaction.[33,37] Bacterial invasion and biofilm formation causes follicular destruction and abscess formation.[33,37] It is proposed that free keratin activates the NLRP3 inflammasome with IL-1 cleavage and IL-1beta secretion.[33,37] Along with IL-23 and IL-6, IL-1b promotes the secretion of innate IL-17 and activation of Th17 cells, which in turn release IL-17, IL-22, and TNF-α.[33,37,39] Residual free keratin perpetuates responses and follicular epithelial strands remaining after cyst rupture form fistulae that harbor bacteria and promote suppuration.[33]

Although the precise cytokine profile and immune pathways are not fully elucidated, various studies demonstrated IL-17, IL-1b and IL-23 increase and implicate the IL-1b-IL-23/ TH17/IL-17 pathway in HS pathogenesis.[33,38,40]

7.2 - Obesity and other endocrine abnormalities

Most HS patients are overweight or obese with a sizable body of literature demonstrating obesity as a paramount risk factor for HS[1,41] and probably also a risk for HS severity.[1] Some factors may explain the pathophysiologic mechanisms behind this association. Adipose cells are capable of secreting proinflammatory cytokines, which may contribute to follicular hyperkeratosis and development of HS lesions.[41] Furthermore, large body folds in obesity increase mechanical stress and promote a warm, humid microclimate favoring bacterial overgrowth which may also have a pathogenic role.[41] A cross sectional study, compared 205 HS patients with a high (above 35) body mass index (BMI) with 246 HS patients with a low BMI (below 25).[42] Those with a high BMI significantly suffered more severe disease (Hurley, PGA, number of areas affected and patient reported severity) and patients with low BMI significantly reported greater severity when they increased their BMI.[42] The authors concluded patients with a low and high BMI could represent two clinically different subtypes of HS suggesting a non-linear relationship between BMI and impact of HS.[42]

The role of androgens and sexual hormones remains controversial,[34] but many facts support a possible relation:
- the typical onset in a narrow age spectrum after puberty;
- rare postmenopausal onset[34];
- usual improvement during pregnancy and post-partum flare-up[34];
- reports of association with irregular menses, hirsutism and higher concentration of total testosterone,[43] although not constant[28,44];
- reports of significant remission after antiandrogen therapy, although most of HS patients have normal androgen profiles[45,46];
- HS in children under 12 is more likely associated with hormonal imbalance, namely adrenal hyperplasia, premature adrenarche, obesity, and metabolic syndrome.[47]

In fact, a diagnosis of HS in children may be a marker of precocious puberty.[47]

7.3 - Smoking

Rates of smoking in HS patients have been noted as high as 42% and 92%.[18,48] An association between HS and current smoking was confirmed in a French cohort of 10 000 subjects but not in former smokers.[26] Conversely, smoking cessation may improve HS.[49]

Smoke components can activate keratinocytes, fibroblasts, and immunocytes, inducing proinflammatory cytokines.[1,38] Additionally, tobacco smoke leads to modification of the skin microflora contributing to biofilm formation and further suppresses the Notch signaling that is already deficient in HS.[38,50,51]

7.4 - Genetics

Up to 40% of patients have a familial history of HS and an autosomal dominant pattern of inheritance has been observed.[1,49,52] Although several genetic loci have been recognized, a single causative gene remains unidentified. Recent genetic studies highlighted the role of the enzyme γ-secretase with heterozygous mutations reported in the γ-secretase genes PSENEN, PSEN1, and NCSTN.[52] These mutations may contribute to 5% of HS cases leading to attenuated Notch signaling, an important modulator of T-cell mediated immune responses, inhibition of the hair growth cycle and conversion of hair follicles into keratin enriched epidermal cysts.[33,38] Additionally, certain TNF gene polymorphisms seem to be associated with HS, which is consistent

with a greater reduction of disease severity after anti-TNF treatment.[53]

7.5 - Mechanical stress

Predisposed HS skin areas are sites of regular mechanical stress.[54] Friction may promote follicular occlusion and rupture of dilated follicles in genetically susceptible patients.[42] One study with histopathology and case reports found increased fragility of the dermoepidermal junction in HS patients, which suggests that friction may contribute to HS development.[54]

7.6 - Microbiology

The efficacy of antibiotics in HS supports a microbial role in its pathogenesis.[55] However, these antibiotics also have anti-inflammatory activity.[55] Therefore, the underlying mechanisms may be more complex.[55,56]

Bacterial collection from superficial lesions has frequently shown negative results or a mixed growth of commensal microbes.[33,57,58] Studies using CO2 laser vaporization of lesional skin level by level or aspirating pus from the deeper parts of HS lesions to prevent contamination by the normal skin microflora, found Gram-positive cocci and rods including *Staphylococus aureus*, coagulase-negative *staphylococci* (CoNS) as *S. epidermidis, Corynebacterium* species and anaerobes of the commensal flora.[1,55] Biofilm formation can also have a role in HS.[56] A retrospective study of 27 patients using histopathology found biofilm-like structures in one-fifth of the samples.[59] It is also possible that chronic HS lesions may resemble an environment such as one produced by a foreign body promoting and maintaining bacterial growth.[56]

No yeasts or other infectious agents were found to play an important role in the pathogenesis. A polymicrobial flora, and, in particular, the dominating *S. aureus*/CoNS in HS lesions, may raise speculations on the pathogenic significance of these recurring bacteriologic findings.[56] Whether bacterial colonization is a primary or a secondary event of an initially sterile process is still a subject of much debate.[56,59]

8. COMORBIDITIES

As a chronic inflammatory dermatosis, HS is associated with a variety of concomitant and secondary diseases.

8.1 - Metabolic

Increasing evidence suggests association with the metabolic syndrome, which may affect more than 50% of HS patients, with subsequently increased cardiovascular risk.[1,18,60] Possible mechanisms behind this association include the long-term effects of the chronic inflammatory state, the sedentary lifestyle of most HS patients, inflammation-induced neuropsychological factors affecting appetite and cortisone levels, and concomitant pharmacotherapy.[18]

8.2 - Inflammatory and rheumatologic

A retrospective study61 found that 38% of HS cases also had Crohn's disease (CD) and a recent study found that 23% of patients with inflammatory bowel disease also had HS.[62]

Several syndromes with pyoderma gangrenosum (PG) and HS have been reported, consisting on a triad of PG, acne conglobata and HS, differentiated clinically by their arthritic component: PAPASH (pyogenic arthritis), PASS (seronegative spondyloarthritis) and PASH (no arthritis).[18,63] Besides, there are many reports of non-syndromic PG and HS.[1,18]

Rheumatologic joint conditions have been reported in association with HS: axial arthritis, peripheral arthritis (including dactylitis), enthesopathies, synovitis-arthritis-pustulosis-hyperostosis-osteitis (SAPHO) syndrome, and specially the spondylarthropathies, sometimes in association with CD.[1,18]

In addition, HS belongs to the group of diseases characterized by follicular occlusion known as the follicular occlusion tetrad: HS, acne conglobata, dissecting cellulitis of the scalp, and pilonidal cysts.[64] Acne vulgaris, keratitis–ichthyosis–deafness syndrome and Dowling–Degos disease have also been associated with HS.[1,18] Scarce data also proposed a link between HS and Down syndrome.[65]

8.3 - Malignancies

HS has been associated with increased risk of cutaneous malignancy.[14,15] A recent revision found 52 cases of squamous cell carcinoma (SCC) published between 1958 and 2009.[66] This can be an underreported complication as in some series the prevalence of SCC in HS was as high as 4.6%.[66] Scheinfeld[67] proposed a possible synergistic effect between chronic inflammation, impaired cellular immunity, and the presence of the human papillomavirus, however this is still under debate.[67]

The association between visceral cancers and HS is more controversial and needs clarification.[1]

8.4 - Depression

There is significant evidence that HS carries a high incidence of depression, with reported rates of 48.1% and 42.9% in 2 cross-sectional analyses,[25,68] although with lower values in other studies.[1,69,70]

8.5 - Other complications

Surprisingly, acute super-infection, including cellulitis and erysipelas, and enlarged lymph nodes are very unusual, with an incidence lower than expected.[1,71]

Lymphatic obstruction and lymphedema, fistulae formation and elephantiasis may complicate long-standing disease.[1]

Other HS complications include anemia, amyloid deposition and kidney failure.[18,72-75]

9. TREATMENT

Treatment varies widely depending on disease severity, with many treatments supported by weak scientific evidence.1 Topical, systemic, and surgical therapies are available and are often used in combination (Table 6).

Table 6 - Hidradenitis suppurativa treatment*.

HIDRADENITIS SUPPURATIVA TREATMENT ACCORDING TO HURLEY STAGE*		
Adjuvant treatment (all stages)	- Weight loss and tobacco cessation - Avoidance of tight-fitting clothing - Pain control - Antimicrobial wash - Appropriate dressings - Management of concomitant comorbidities	
Hurley Stage I and II	Topical treatments	- Topical antibiotics and keratolytic agents (e.g. clindamycin lotion 1% bid for 3 months; resorcinol 15% bid) - Intralesional corticosteroids
	Systemic treatments	- Oral antibiotics (e.g. oral tetracycline 500 mg bid for 4 month; dapsone 25-200 mg daily) - Systemic retinoids (e.g. acitretin 0.25 to 0.88 mg/kg daily; alitretinoin 10 mg daily) - Antiandrogenic therapies (e.g. oral contraceptive pills; finasteride 5mg daily; metformin 500-1500 mg daily)
	Surgical/ physical treatments	- Less invasive surgical approaches (e.g. local excision, curettage and electrocauterization, deroofing, cryoinsufflation) - Laser and lights therapy (e.g.Nd:YAG, CO2 laser, IPL, PDT, PUVA)
Hurley Stage II to III (includes Stage I to II approaches)	Systemic treatments	- Oral antibiotics (e.g. oral rifampin 600 mg daily + clindamycin 300 mg bid for 10 weeks) - Systemic immunosuppressants (e.g. ciclosporin 2-6 mg/kg/day) - Biological treatments (e.g. adalimumab160 mg week 0, 80 mg week 2, then 40 mg weekly. Consider also, infliximab 5 mg/kg weeks 0, 2 and 6; ustekinumab 45 or 90 mg at weeks 0, 4, 16 and 28; and anakinra 100 to 200 mg daily)
	Surgical/ physical treatments	- More invasive surgical approaches (e.g. wide radical excision)

* Adapted from Danny Barlev *et al*[23].
CO2: carbon dioxide; Nd:YAG: long-pulsed neodymium:yttrium-aluminum-garnet laser; IPL: intense pulse light; PDT: photodynamic therapy; PUVA: bath psoralen plus ultraviolet A.

9.1 - General measures

Based on pathophysiological mechanisms, the general expert opinion proposes weight loss, smoking cessation, avoidance of tight-fitting clothing and management of concomitant comorbidities,[1] however, there is no consistent data to prove the benefit of these measures. Although frequently recommended, studies to support the routine use of topical aseptic washing and dressings of involved areas are lacking.[76,77]

9.2 - Topical therapy

Topical keratolytic agents and topical antibiotics have been used in the management of patients with mild HS, based on the possible involvement of follicular occlusion and the role of bacteria.[1] Topical resorcinol 15% is an exfoliant with keratolytic, antipruritic, and antiseptic properties. In one prospective study enrolling 12 women with mild HS there was a significant pain decrease and reduction in mean duration of painful abscesses in all patients.[78] The European guideline on HS recommended the application of a lotion containing clindamycin 1% b.i.d. for 3 months in patients with localized Hurley Stage I or mild stage II disease, since clindamycin is the only antibiotic studied as a topical agent.[1]

Intralesional corticosteroids are widely used for the management of acute flares of single or limited number of inflammatory nodules and may also be helpful for the treatment of recalcitrant nodules and sinus tracts.[76,79] Recently, Riis *et al*,[80] conducted a prospective multicenter study including 36 patients (3 lost to follow-up), to assess the outcomes of routine intralesional triamcinolone (0.2-2.0 mL, mean 0.75 mL of a 10 mg/mL solution) on nodules or abscesses. Authors found a significant reduction in physician-assessed size, edema, redness, and suppuration after a mean of 6.9 days. A significant difference in patient-reported pain visual analog scale scores occurred after 1 day.

The efficacy of botulinum toxin injections for HS has been reported in 3 cases with positive results in 2.[81,82]

In addition, topical retinoids, azelaic acid or fusidic acid also have been used in limited cases.[1,79]

9.3 - Systemic therapy

Systemic treatment is indicated when more severe or widespread lesions are present (Hurley stage II and/or III) or during acute flares.[1]

9.3.1- Systemic antibiotics

Systemic antibiotics are the most often prescribed drugs for HS.[83-85] Oral tetracyclines (doxycycline 100 mg bid, minocycline 100 mg bid and tetracycline 500 mg bid) for up to 4 months are often used for mild to moderate HS, although published data regarding their efficacy is limited.[23,83]

The efficacy of a combination of rifampin 600 mg and clindamycin 600 mg administered in a single or in 2 divided daily doses for 10 consecutive weeks is documented in several studies (total number of patients, 141) with an average of 81% (range, 71% - 85%) of subjects obtaining some response.[83,86-89] However, the interpretation of these results should be made with caution since the definition of HS severity and response to treatment varied between studies.[83]

In a retrospective study the combination of rifampin (10 mg/kg once daily), moxifloxacin (400 mg daily) and metronidazole (500 mg t.i.d.), either alone or preceded by systemic ceftriaxone (1 g daily) was effective in 16 of 28 patients with Hurley stage II and III disease.[90] Main adverse events of the treatments were gastrointestinal disorders (64% of patients) and vaginal candidiasis (35% of females). Reversible tendinopathy and hepatitis occurred in 4 and 1 patient, respectively.

9.3.2 - Retinoids

The remote similarities of HS and acne vulgaris led some clinicians to use retinoids for the treatment of HS.[34] Isotretinoin achieves its efficacy by influencing cell-cycle progression and cellular differentiation, and particularly by induction of apoptosis in sebaceous gland cells.[34] However, reduction of sebaceous gland size and inhibition of sebaceous gland activity is not a good adjuvant for HS treatment, since the volume of the sebaceous glands seems to be *a priori* reduced in this disease.[34] Accordingly, the effect of isotretinoin is often disappointing and this drug is not recommended for HS.[1,34] On the other hand, acitretin that contributes to normalization of cell differentiation and thinning of the cornified layer through direct reduction of keratinocyte proliferation rate, has been successfully used[34] in doses ranging from 0.25 to 0.88 mg/kg with reported efficacy rates between 50% and 80%.[1,23,91] Acitretin is indicated in the early HS stages but can also be advocated in the chronic stages with recurrent abscesses with sinus tracts and scarring.[1]

Alitretinoin has a pharmacologic mechanism similar to acitretin, but a much shorter half-life and, thus, teratogenic risk is not so long lasting.[92] Verdolini *et al*,[92] found a significant improvement (78.5%) after treatment with alitretinoin (10 mg daily) for 24 weeks in 14 females of child-bearing age.

All retinoids are known for their teratogenic potential, therefore contraindicated during pregnancy or breast-feeding, and used with contraception during child-bearing age.[1]

9.3.3 - Systemic corticosteroids

In HS patients with significant flares, short courses of systemic corticosteroids (0.5-0.7 mg/kg oral prednisolone) may be used as rescue therapy, but routine long-term use is not currently recommended.[1,79]

9.3.4 - Cyclosporin and other conventional immunosuppressive therapies

Cyclosporin is a calcineurin inhibitor with potent immunosuppressive activity which specifically targets T lymphocytes.[1] Few case reports have documented a good response to cyclosporine in patients with severe HS, with treatment dosage of 2-6mg/kg used for 6 weeks-7 months.[93-95] It should be reserved for cases after failure of first, second and third line therapies.[1]

Methotrexate was reported to be ineffective in a series of 3 patients with severe HS.[96] Clinical reports to support the use of other immunosuppressive therapies, such as azathioprine and mycophenolate mofetil, are lacking.[83]

9.3.5 - Biologic agents

Biologic agents have been increasingly used in the management of moderate to severe HS. Several molecular-targeted anti-inflammatory drugs, including agents blocking the effect of TNF-α, IL-1, IL-12/23, IL-17a and an anti--CD20 monoclonal antibody have been used.

Adalimumab is a monoclonal antibody that blocks the biological effect of TNF-α.[1] Two phase III multicenter trials of adalimumab were recently completed, PIONEER I and II, enrolling 633 patients.[97] Clinical response rates at week 12 were significantly higher for the groups receiving adalimumab 40 mg weekly than for the placebo groups: 41.8% versus 26.0% in PIONEER I and 58.9% versus 27.6% in PIONEER II.[97] The differences between the two trials could be related to the fact that in PIONEER I, patients receiving oral antibiotics had to stop treatment for at least 28 days before baseline whereas in PIONEER II they were allowed to continue treatment with antibiotics (tetracycline class) in stable doses. Adalimumab 160 mg week 0, 80 mg week 2, then 40 mg weekly since week 4 is currently approved for the treatment of moderate to severe HS. Adalimumab every other week seems less effective than weekly.[8]

Infliximab is a chimeric monoclonal antibody against TNF-α. A systematic review of 147 patients treated with infliximab (mostly 5 mg/kg at weeks 0, 2 and 6) found a significant improvement in 50% of patients and 39% more showed moderate improvement.98 The majority of patients received maintenance therapy every 6–8 weeks.[98]

Etanercept is considered inefficacious for HS.[1,23]

Ustekinumab, an anti-IL-12/IL-23 antibody, has also been used (45 or 90 mg at weeks 0, 4, 16 and 28) with good results.[99] In a prospective study, out of 17 treated patients, 35%, 47% and 12% had a marked, moderate and no improvement at week 40, respectively.[99]

Recently a clinical trial studied the efficacy of anakinra, an antibody directed against IL-1, in severe HS.100 A

positive HiSCR at 12 weeks was achieved in 3 of 10 patients on placebo and in 7 of 9 on anakinra.[100] Additionally, at least 10 more patients have been reported, with 7 showing a response to 100 to 200 mg anakinra on daily subcutaneous doses.[101] Canakinumab, another anti-IL-1, also demonstrated good response.[102]

Successful treatment of severe recalcitrant hidradenitis suppurativa with the interleukin-17a antibody secukinumab was recently reported.[103]

A successful response was also reported with the monoclonal antibody anti-CD20 rituximab (two courses of 200 mg) in a patient with idiopathic carpotarsal osteolysis and chronic active antibody-mediated rejection.[104]

Investigations are currently ongoing or recruiting for diverse biologic agents, such as CJM112 (a fully human anti–IL-17A mAb [NCT02421172]) and MABp1 (human anti–IL-1a antibody in patients with HS refractory to adalimumab [NCT02643654]).[105]

Paradoxically, HS induced by biologic agents (including adalimumab, infliximab, etanercept and rituximab) has also occasionally been reported.[106]

9.3.6 - Antiandrogenic therapy

Although it is a controversial topic, several data show that antiandrogens, such as cyproterone acetate, and estrogens improve HS, while progestogens induce or worsen HS.[107]

The competitive and selective inhibitor of the type II isoenzyme of 5α-reductase, finasteride (5mg/day) used as monotherapy or adjunctive therapy has shown encouraging and remarkable results in small case series, including complete remission.[42-108] Randhawa *et al*[109] used finasteride as adjunctive therapy with significant improvement in a 7 years-old child and two 15 years-old adolescents, all female, 2 of them with concomitant endocrine disorders. Recently, Mota *et al*,[110] reported five cases of children with HS Hurley I (4 girls and 1 boy, diagnosed between the ages of 6 and 11 years) treated with oral finasteride as monotherapy (increasing dose up to 5 mg/day) with overall improvement and no adverse effects, but 2 patients relapsed after stopping treatment.

Metformin exerts an antiandrogenic effect by reducing ovarian overproduction of androgens.[79] In a clinical trial, 18 of 25 (72%) patients who received metformin (500 to 1500 mg daily) had a mean 12.7 reduction in their Sartorius score at 24 weeks while 7 patients had no response.[111]

Antiandrogenic therapy can be considered in patients with HS who also have diabetes or women with menstrual abnormalities, signs of hyperandrogenism or polycystic ovary disease.[1,83]

9.3.7 - Other systemic treatments

Dapsone: In a retrospective review of 24 patients,[112] a slight or significant clinical improvement was observed in 9 (38%), but no one with severe disease (Hurley Stage III) responded. Therefore, dapsone, 25-200 mg a day, should be reserved for patients with mild to moderate disease (Hurley stage I or II).[1]

Zinc Gluconate: A study of 22 patients with mild to moderate HS receiving zinc gluconate (90 mg/day) for at least 6 months demonstrated a complete remission in 36% of the patients.[113]

Intramuscular gamma-globulin (IgG): Four out of five HS patients demonstrated 50-70% improvement in 1 retrospective case series.[114]

Tacrolimus: In 2 patients with a kidney transplant and comorbid HS, all lesions disappeared after a switch from cyclosporine to tacrolimus while maintaining mycophenolate.[115,116]

Fumarates: In one prospective case series, 3 out of 7 patients with moderate to severe HS had a meaningful improvement.[117]

Staphage lysate: In a study of 31 patient's treatment with staphage lysate (obtained by bacteriophage lysis of *Staphylococcus aureus*) was of greater benefit than placebo.[118]

Colchicine: Although the efficacy of colchicine is reported as poor and not recommended,1 recently, a prospective series of 20 HS patients (10 women and 10 men) treated with minocycline (100 mg/day) in combination with colchicine (0.5 mg twice daily) for 6 months followed by a maintenance regimen of 0.5 mg colchicine twice daily for 3 months, showed a significant improvement as reflected in Hurley scoring system, Dermatology Life Quality Index questionnaire and physician's global assessment scale (patients achieved substantial improvement or complete remission).[119]

9.4 - Surgical Therapy

Since most common non-surgical methods seldom result in a long-lasting cure, surgical treatment seems to be a quite common and accepted therapeutic modality.[1] As surgical wounds heal best if inflammation is reduced beforehand, antibiotics, especially those with anti-inflammatory properties, can be supplemented with short courses of prednisone, cyclosporine, or biologic agents to reduce tissue inflammation in patients with severe disease.[120] Recently, the role of noninvasive imaging techniques, as ultrasound and MRI, has been highlighted to guide surgeons in the complete removal of chronic HS lesions.[11]

Local destruction of individual small lesions may be attempted. In fact repeated electrocauterization and curettage of the draining sinuses may be curative.[1] Deroofing, in which the roof of a sinus tract is surgically removed and the floor of the lesion is left exposed to heal by second intention, has emerged as one of the most effective methods for HS treatment, with 83% of 73 patients showing no recurrence after a median follow-up of 34 months.[121] Recently, Blok *et al*,[122] described the promising skin-tissue-sparing excision with electrosurgical peeling (STEEP) technique for Hurley stage II–III disease, performed under general anesthesia. In contrast to wide excisions that generally reach the deep subcutaneous fat, in STEEP the fat is maximally spared by performing successive tangential excisions of lesional tissue until reaching the epithelialized bottom of the sinus tracts. In addition, fibrotic tissue is completely removed in the same

Table 7 - World Health Organization pain ladder*.

Step 1	Mid pain			Non opiod	+	Optional adjuvant	If pain persists or increases go to step 2.
Step 2	Moderate pain	Weak opioid	+	Non opiod	+	Optional adjuvant	If pain persists or increases, go to step 3.
Step 3	Severe pain	Strong opioid	+	Non opiod	+	Optional adjuvant	Freedom from pain.

*Adapted from Stjernsward J.[140]

manner. The healthy tissue at surgical margins is injected with triamcinolone acetonide 10-20 mg and bupivacaine 0.5% (10 mL) to prevent hypergranulation and surgical wounds are left open to heal by secondary intention. This tissue-sparing technique results in low recurrence rates, high patient satisfaction with relatively short healing times and favorable cosmetic outcomes without contractures.[122]

Patients with chronic and extensive Hurley stage III disease, if not amenable to deroofing, may be managed by wide excision of the entire affected area.[120] After extensive tissue removal, the different options regarding closure will influence both the esthetic outcome and recurrence rate. Even large surgical defects may be allowed to heal by secondary intention, without contractures or reduced range of motion, with success rates as high as 89% - 72% at 1 year.[1,120,123] Another systematic review found 15% recurrence rate for primary closure, 8% for flaps, and 6% for grafts, after wide local excision.[124]

Pagliarello *et al*[125] recently described a new technique, cryoinsufflation, a modified spray cryotherapy performed by injecting liquid nitrogen through a needle directly into HS tracts with good results.

9.5 - Lasers and Lights

Various laser and light treatments have been suggested in HS management.

CO2 laser ablation is an efficacious treatment with recurrence rate varying from 2 of 185 sites to 2 of 9 patients.[126,127]

Long-pulsed neodymium: yttrium-aluminum-garnet laser (Nd:YAG) designed for hair removal, has been tried in the treatment of HS lesions and background skin, based on the assumption that HS starts in the hair follicle.[1] Reported improvement rates range from 31.6% to 72.7%.[128,129]

Intense pulse light (IPL) used in a prospective trial of 18 patients, showed a 55% reduction of the Sartorius score compared to 10% on the untreated side.[130]

Photodynamic therapy (PDT), reported in more than 20 HS patients,[1] has been described to have good to mediocre efficacy.[131-134]

In a retrospective trial with 13 patients bath psoralen plus ultraviolet A (PUVA) twice weekly, 5 patients had clearance or near clearance of their lesions, 4 had moderate clearance, and 4 had minimal to no response.[135]

9.6 - Radiotherapy

Several series of patients have been treated with radiotherapy with moderate results. Considering the spontaneous high risk of cancer in HS patients, this potentially carcinogenic treatment should be considered with caution.[136]

9.7 - Pain management

The management of pain in patients with HS is complex and controlled trials are lacking. A multidisciplinary approach that features collaboration with a pain specialist is vital to achieve optimal care.[137] Chronic pain management in patients with HS should follow the World Health Organization pain ladder (Table 7).[1,137] Oral paracetamol and nonsteroidal anti-inflammatory drugs are considered first-line agents, but if insufficient, oral opiates may be selected.[137] Pregabalin, gabapentin, tricyclic antidepressants and selective serotonin reuptake inhibitors can offer long-term pain control.[137]

10. PROGNOSIS

There is no definitive consensus but HS severity seems greater among males.[22] and involved areas also differ between genders, with the groin and submammary regions most commonly affected in women while the buttocks and perianal skin are the most affected areas in men.[22]

Chronicity is the rule in HS. In a questionnaire survey the mean duration of the active disease was 18.8 years.[138] However, disease tends to become less active among females in their 50s and is usually in complete remission after menopause. In males, HS may continue to be active in old age.[136]

As a chronic inflammatory dermatosis, HS is associated with a variety of concomitant and secondary diseases, namely metabolic syndrome, several inflammatory and rheumatologic disorders, depression, increased risk of malignancy and other complications.[1] Recently, Egeberg *et al*,[139] reported a study comprising 5964 HS patients without CV history (from the national register of Danish patients) matched to 29,404 controls from the general Danish population with no CV background. Compared with the general population the risk of myocardial infarction (MI), ischemic stroke, CV-associated death and all-cause mortality was significantly increased in HS patients after adjustment for confounding factors and the risk of MI, ischemic stroke, and all-cause mortality was similar to that of patients with severe psoriasis, however, the risk of CV associated death was significantly higher in HS patients with HS than in psoriatic patients.[139] These novel findings suggest that HS is an independent risk factor for adverse CV outcomes.[139]

CONCLUSION

HS is a chronic and recurrent skin disease with significant

associated psychosocial morbidity. Reflecting the lack of an established pathogenic pathway, treatments for HS remain suboptimal. A growing body of research and evidence, however, is paving the way for better management of patients with this difficult condition. Often HS management requires a multidisciplinary team and the team leader should be a dermatologist.

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Educação Médica Contínua

VERIFIQUE O QUE APRENDEU

1. **Relativamente à hidradenite supurativa (HS) assinale a afirmação falsa:**
   a) É uma dermatose inflamatória crónica do folículo piloso, sendo a inflamação das glândulas sebáceas a este associadas, o primeiro passo da sua etiopatogenia
   b) Os critérios de diagnóstico estão bem estabelecidos
   c) A etiologia é provavelmente multifatorial, envolvendo fatores genéticos, tabagismo, stress mecânico, obesidade, resposta aberrante imune e anormalidades hormonais
   d) A abordagem da HS requer uma equipa multidisciplinar

2. **Relativamente à hidradenite supurativa (HS) assinale a afirmação verdadeira:**
   a) Os mecanismos etiopatogenicos estão bem estabelecidos
   b) Apesar da maioria dos doentes terem excesso de peso, a obesidade não parece desempenhar um papel importante na etiopatogenia da HS
   c) O tabagismo parece desempenhar um papel protetor
   d) A via IL-1b-IL-23 / TH17 / IL-17 foi recentemente implicada na etiopatogenia da HS

3. **Relativamente ao tratamento da hidradenite supurativa (HS) assinale a afirmação verdadeira:**
   a) O tratamento tópico nunca deve ser utilizado isoladamente na abordagem aos doentes com HS
   b) A administração de isotretinoína está associada a uma melhoria em cerca de 40% dos doentes com HS, sendo assim recomendada para doentes com HS moderada a grave.
   c) Os fármacos mais prescritos no tratamento dos doentes com HS são os do grupo dos retinóides
   d) A abordagem da HS varia amplamente dependendo da gravidade da doença, sendo a maioria dos R: d

4. **Relativamente à hidradenite supurativa (HS) assinale a afirmação verdadeira:**
   a) As áreas preferencialmente afetadas tendem a ser as mesmas em homens e mulheres
   b) A doença tende a ficar menos ativa após a quinta década quer nos homens quer nas mulheres
   c) Recentemente a HS foi associada a um risco significativamente aumentado de eventos cardiovasculares adversos e de mortalidade por todas as causas
   d) Apesar dos doentes com HS terem um risco cardiovascular aumentado este parece ser significativamente menor do que aquele observados nos doentes com psoríase.

Chave: 1.a); 2.d); 3.d); 4.c)