

Consensus on the treatment of hidradenitis suppurativa – Brazilian Society of Dermatology*

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DOI: http://dx.doi.org/10.1590/abd1806-4841.20198607

Abstract: Hidradenitis suppurativa is a chronic immune mediated disease of universal distribution that causes great damage to the quality of life of the affected individual, whose prevalence is estimated at 0.41% in the Brazilian population. The objective of this work was update on physiopathogenesis, diagnosis and classification of hidradenitis suppurativa and to establish therapeutic recommendations in the Brazilian reality. It was organized as a work group composed of eight dermatologists from several institutions of the country with experience in the treatment of hidradenitis suppurativa and carried out review on the topic. Recommendations were elaborated and voted by modified Delphi system and statistical analysis of the results was performed. The Brazilian consensus on the clinical approach of hidradenitis suppurativa had the support of the Brazilian Society of Dermatology.

Keywords: Anti-bacterial agents; Antibodies, monoclonal; Consensus; Hidradenitis suppurativa

INTRODUCTION

Hidradenitis suppurativa (HS) is a universally distributed chronic inflammatory condition that leads to a great impairment in the life of those affected, with an estimated prevalence of 1% to 4% of the population. In Brazil, the prevalence is 0.41%, with no difference between the many regions in the country, being more prevalent among adolescents (0.57%) and adults (0.47%) than in children (less than 0.03%), according to a study based on a telephone survey with more than 17,000 people from 87 municipalities. 2

OBJECTIVE OF THE CONSENSUS

The objective of this consensus is to inform the physician about HS and provide recommendations on its treatment according to the Brazilian context. It is not a systematic review but a docu-

ment that integrates the newest immune-inflammatory concepts, taking into consideration the classification, investigation and treatment based in evidence from the literature, guided by international guidelines and validated by Brazilian specialists with the modified "Delphi" system.³ The differences in practice between men, women, adults and children are also one talking point.

To prepare this consensus, a work group made by eight dermatologists was formed with the support of the Brazilian Society of Dermatology, who are experienced in the clinical and surgical treatment of patients with hidradenitis suppurativa, representing the many regions of the country. A systematic review of the clinical treatment of hidradenitis suppurativa and a survey of therapeutic guidelines were performed.

Received 07 July 2018.

Accepted 13 September 2018.

- * Work conducted at the Sociedade Brasileira de Dermatologia, Rio de Janeiro (RJ), Brazil. Financial support: None.
 - Conflict of interest: The members of this council declare they took part in scientific meetings, lectures and/or received support for events of the following pharmaceutical companies: Renata Ferreira Magalhães: Abbvie, Janssen-Cilag, Pfizer, Novartis and Lilly. Maria Cecília Rivitti-Machado: Abbvie and Bayer. Gleison Vieira Duarte: Abbvie, Janssen-Cilag, Leo Pharma, Galderma, Bayer, Pfizer, Novartis and Biolab. Roberto Souto: Abbvie, Novartis, Janssen-Cilag, Pfizer and Lilly. Daniel Holthausen Nunes: Abbvie, Janssen-Cilag, Novartis, Pfizer and Sanofi. Mario Chaves: Abbvie. Sérgio Henrique Hirata has no conflict of interests. Andrea Machado Coelho Ramos: Abbvie, Janssen-Cilag, Novartis and Sanofi.
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Recommendations based on evidence were established, arranged into a poll system (Survey Monkey®) and forwarded to the specialists. For the topics "general measures" and "topical treatments" and for the topic "immunobiologics", polls through the modified Delphi system (RAND/UCLA) were conducted, where agreement was indicated with the statements (1=totally agree; 2=partially agree; 3=do not agree or disagree; 4=partially disagree; 5=totally disagree). The recommendations that achieved more than 75% of agreement among the specialists were included. The remaining were re-evaluated, re-discussed and re-posted for voting for the second time. Data obtained were analyzed statistically.^{3,4} For the topic "systemic treatments", a ranking according to the order of preference among the drugs that should be used for the treatment of HS was asked of the specialists. To verify differences in the specialists' preferences, the Friedman test was used, and the significance level adopted was of 5%. The sample was obtained by nomination and subjected to the randomness test, which resulted in the non-rejection of randomness, with a significance level of 5%.5

Data were arranged into tables with levels of evidence (Center of Based Evidence Oxford 2001), grades of recommendation and degree of agreement among the specialists.⁶

DEFINITION

Hidradenitis suppurativa is a chronic, recurrent inflammatory condition of the hair follicle, that occurs in genetically predisposed individuals and is influenced by environmental factors such as smoking and obesity. It causes a great impact in the quality of life with physical, psychological and socioeconomic sequelae.¹

The physiopathogenesis of the disease is currently understood as: I) hyperkeratosis and follicular occlusion; II) dilatation of the pilosebaceous unit; III) rupture and release of the follicular contents into the dermis; IV) secondary inflammatory reaction; V) influx of inflammatory cells and release of new cytokines, perpetuating the process (raise in TNF α , IL-6, IL-10, IL-12, IL-23 and IL-17); with the formation of abscesses and fistulas. Sex steroids seem to influence the course of the disease with onset after puberty, female predominance and perimenstrual exacerbation; however, their contribution to the pathogenesis is still unclear. ^{1,7,9}

COMORBIDITIES

Hidradenitis suppurativa can be associated to many diseases, such as follicular occlusion syndrome (acne conglobata, dissecting cellulitis and pilonidal sinus); auto-inflammatory diseases such as SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis), PASH (pyoderma gangrenosum, acne and suppurative hidradenitis) and PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis) syndromes and genetic syndromes, the most prevalent being Down and KID (keratosis, ichthyosis, deafness) syndromes. It is also frequently associated to inflammatory bowel disease and spondyloarthropathies. It can be accompanied by manifestations of neutrophilic conditions such as pyoderma gangrenosum, Sweet syndrome and erythema nodosum. Psychiatric conditions are highly prevalent in HS patients, such as depression and suicidal ideation. More than half of the patients are obese and

present features of metabolic syndrome, including insulin resistance and polycystic ovary syndrome, which are more prevalent in affected females. ¹⁰⁻¹³ HS patients are under a higher risk of early severe cardiovascular events and reduced life expectancy than patients with psoriasis and other severe inflammatory diseases. ¹⁴

The dermatologist should be vigilant and inquire about possible symptoms of these entities (joint pains, bone pains, intestinal symptoms, sexual dysfunction, psychiatric symptoms) so that the approach to the HS patient be comprehensive.¹⁵

DIAGNOSIS

Diagnosis is clinical in essence, based on the modified criteria of Dessau. For such, it is important to define **lesions** and **typical sites** besides recurrence or chronicity, translated by the occurrence of 2 or more episodes in 6 months.^{1,16} For didactic purposes, this consensus suggests the following description for HS lesions:

Nodule: raised, palpable, edematous lesion, larger than 1 cm. Abscess-like: painful, fluctuant lesion larger than 1 cm in diameter, with an inflammatory aspect, not necessarily septic.

Tunnel: longitudinal, raised, painful, fluctuant mass, with variable length and depth, ending on the skin surface and occasionally with fluid discharge (pus, blood, serum). This denomination includes fistulas, draining and non-draining sinus tracts.

Typical sites are axillae, inguinal regions, inframammary region and intermammary and gluteal clefts, even though atypical sites can also be involved (face, neck, back, thighs).¹⁷

Complementary exams such as biopsy and culture of the lesions are indicted in cases of diagnostic uncertainty. ¹⁸ Suspicious chronic lesions can also require malignancy screening. ¹⁹ Imaging studies (ultrasound and nuclear magnetic resonance) can be beneficial for a better characterization of the lesions and/or surgical programming. Ultrasound evaluation can contribute to post-surgery follow-up if recurrence is suspected. ²⁰

OBJECTIVES OF MEDICAL TREATMENT

Control the inflammation and intercurrent infections;

Avoid progression to advanced stages with fibrosis and scarring and involvement of extensive and/or multiple areas;

Improve quality of life, particularly in regards to pain and discharge;

Prepare for surgical procedure, reducing inflammation and delimitating the lesion;

Approach extensive, disseminated, ulcerated and/or surgically difficult-to-treat clinical forms;

Treat syndromic cases, in which HS is associated to other conditions such as auto-inflammatory diseases and inflammatory bowel disease.

CLASSIFICATION

To define the treatment to be established, is important to recognize elementary lesion and adequately classify HS. Many classifications were proposed, but the following classifications were chosen to guide this consensus due to their practicality and ease of use:

Hurley Stages

Hurley's classification, the oldest one, allows for the prompt and intuitive evaluation but has limitations such as not including the location and number of affected sites, of not reflecting the inflammatory stage and not allowing follow-up (Chart 1). Thus, other classification/staging criteria are necessary to determine the severity of the clinical picture. ^{21,22}

International Hidradenitis Suppurativa Severity Scoring System (IHS4)

This system was recently developed and validated by members of the European Hidradenitis Suppurativa Foundation and consists in a simple evaluation that better reflects the severity of the clinical picture:

IHS4 = number of nodules (multiplied by 1) + number of abscesses (multiplied by 2) + number of draining tunnels (multiplied by 4);

The total value is stratified as mild (score of 3 or less), moderate (score of 4 to 10) and severe (score of 11 or more). 23

Hidradenitis suppurativa score (HiSCR)

This scale was developed with the purpose of being a parameter of evaluation of the clinical response to treatment. The definition proposed of response to treatment (i.e., HiSCR reached) is when there is at least a 50% reduction in the sum of abscesses and inflammatory nodules, with no increase in the number of abscesses and tunnels with or without inflammatory activity when compared to the baseline count. $^{24}\,$

Clinical classification

Besides the severity assessment indexes, hidradenitis should be understood according to its clinical features that can influence the treatment choice. Canoile-Poitrine classification groups cases into axillary-mammary, follicular and gluteal types.²⁵ Van der Zee *et al* proposed the classification into the regular, conglobata, scarring folliculitis, frictional furuncle, syndromic and ectopic types, suggesting this can even help guide treatment choice.²⁶

TREATMENT

STEP 1

General measures

Weight control

There are studies correlating obesity with the course and severity of HS. The influence of obesity in the process of systemic inflammation and risk of comorbidities is known. In the case of HS, obesity influences the disease directly through mechanical effects

CHART 1: Hurley's classification for hidradenitis suppurativa Hurley staging Stage I Single or multiple abscesses, without tunnels or scarring Stage II Single or multiple isolated recurrent abscesses, with the formation of tunnels and scarring Stage III Multiple interconnected tunnels and abscesses involving at least one whole anatomic region

(friction, rubbing of the hair shaft) and the coexistence of hormonal changes (polycystic ovary syndrome and glucose intolerance). In view of these considerations, weight loss is recommended in the approach of the patient with HS, with or without disease activity.²⁷⁻³⁰

Management of pruritus

It is not common to ask about pruritus when seeing patients with HS. However, great part of the patients complain of pruritus that can even impair sleep and, consequently, the quality of life. Studies demonstrate that pruritus, as erythema and local pain are considered prodromal symptoms for flares. Pruritus control is recommended with or without disease activity, with the primary goal of improving the quality of life of these patients.^{31,32}

Smoking

Even though there are no randomized studies establishing the causal relationship between smoking and HS, many studies point to a high prevalence of smoking among HS patients, besides increased severity of the disease in those who smoke. Tobacco seems to influence the genetic predisposition for HS, leading to the formation of follicular plugs and the inflammatory process triggered by neutrophils. Smoking cessation is important in the approach of the patient with HS. 33-36

Friction

Studies demonstrated the impact that friction has on the stability and distortions of the hair follicle even before the formation of the follicular plug. The predilection of HS to flexural areas is clear, as well as a higher prevalence in obese patients. Restricting the use of tight clothing and/or clothing that causes friction in the areas of predilection for HS lesions is recommended. 37,38

Local antiseptics

It is known that HS is an inflammatory disease and when an infectious process occurs it is secondary. There is the hypothesis that follicular occlusion could be a site for bacterial colonization, triggering an exacerbated inflammatory reaction to the local microbiome. Advice on adequate local hygiene should be given, although there is no need to exhaustively remove germs or to use soaps with high concentrations of chlorhexidine. ³⁹⁻⁴³

Hair removal

Laser hair removal leads to the reduction in the number of hair follicles and bacteria in the affected areas. It is an adjuvant therapy for the management of HS, reducing the number of flares and preventing the appearance of new lesions.

Many studies have showed that laser hair removal is effective in the control of HS. A controlled, randomized, prospective study with 22 patients Hurley I to III using Nd:Yag laser demonstrated a 65% improvement after three monthly treatments.⁴⁴ Another randomized study compared contralateral sites as controls and reduction in HS severity was of 65.3% and 72.7% after laser treatment when compared to 7.5% and 22.9% for control sites treated topically with 10% benzoyl peroxide and 1% clindamycin.⁴⁵ Other lasers, such as diode and intense pulsed light have successful reports in smaller

series of patients.3

Dressings

HS patients can present with discharge despite adequate treatment, causing psychosocial and physical discomfort due to odor and maceration. Dressing should be adapted to the anatomic location of lesions and have absorbent and non-irritant properties, besides keeping the surface dry and absorb odor. There are no specific dressings used in the treatment of HS nor controlled, randomized studies assessing the use of specific dressings or methods for treating wounds in the treatment of HS.46,47

Topical treatments

Clindamycin

One percent clindamycin gel is the only topical antibiotic with randomized studies comparing its efficacy to the use of a systemic medication, tetracycline. There was no difference in efficacy after 3 months of treatment. During the use of topical clindamycin, superficial lesions (pustules, folliculitis) showed better responses when compared to deeper lesions (nodules and abscesses). In view of these considerations, the use of 1% clindamycin gel in HS lesions is recommended for Hurley stage I or in cases with superficial lesions during exacerbation periods.⁴⁸⁻⁵⁰

Fusidic acid

The use of fusidic acid was evaluated through case reports and one prospective study where Hurley stage I patients were assessed. They were submitted to conservative therapy with fusidic acid, besides local antiseptics until the inflammatory nodules were under control, and more than 70% of cases achieved control.⁵¹ Comparing with gentamicin and mupirocin, fusidic acid has a higher minimum inhibitory concentration in the deeper layers of the skin. In view of these considerations, the use of fusidic acid in HS lesions can be useful for Hurley stage I.^{51,52}

Other topical antibiotics

There are not enough studies to support the use of gentamicin or erythromycin in HS. Some studies evaluated the use of gentamicin for the postoperative period with the aim of assessing the rates of recurrence and local complications. A reduction in short-term complications was seen (8 weeks); however, there was no success in the long-term rates of recurrence.⁵³ The use of gentamicin in HS lesions would only be indicated if the use of other topical antibiotics was not possible.

Benzoyl peroxide associated to clindamycin

Topical treatment with 10% benzoyl peroxide gel associated to 1% clindamycin gel or lotion was compared to the topical treatment associated to Nd-Yag laser hair removal in a controlled, prospective study with 22 Hurley I to III patients. Progressive improvement in the activity of the disease was seen, more markedly during the 4 months of treatment, which was maintained in the post-treatment 2-month follow-up period. The improvement was of 72.7% on the side treated with laser and 22.9% on the control side, suggesting that topical treatments improve HS, although less than

when associated to laser hair removal. There are no studies with benzoyl peroxide alone 45,46

Topical retinoid

Some specialists suggest the use of adapalene, azelaic acid, antiseptics or other acne treatments can be beneficial; however, evidence is lacking to indicate such treatments.^{3,54,55}

Resorcinol cream

Topical resorcinol was studied in a prospective study. Twelve patients with Hurley I or II HS were instructed to apply 15% resorcinol cream twice daily on the active HS lesions. In all patients, the use of resorcinol resulted in reduction of pain and reduction in the mean duration of painful abscesses. Topical resorcinol (m-dihydroxybenzene) is an exfoliant with keratolytic, antipruritic and antiseptic activity. It can be useful to shorten the mean duration of a painful nodule or abscess. There are still no controlled, randomized studies on its efficacy.

Intralesional steroid

Intralesional triamcinolone acetonide in the concentration of 5 to 10mg/mL is used for the treatment of acute inflammation and abscesses. It can also be useful for the treatment of refractory nodules and tunnels. Clinical response is fast, within 48 to 72 hours. Well-known adverse events such as atrophy, pigment changes and telangiectasias can occur but, if used in the recommended doses, systemic adverse events are uncommon. This treatment is contraindicated if infection is present. Intralesional steroid injection is seen as beneficial by physicians and patients in the management of HS, reducing pain after 1 day and inflammatory signs after 7 days. 346.57.58

STEP 2

Systemic treatment

Children younger than 12 years of age

Studies show that 36% of HS cases occur before 20 years of age; this *datum* is controversial, ranging from less than 2% of cases before 11 years of age to 7.6% before 13 years.⁵⁹⁻⁶¹ However, only studies with low levels of evidence are available for the treatment of HS in the pediatric age group.

The use of systemic antibiotics is based in clinical trials in adults. Different case series of HS in children identified oral erythromycin and clindamycin among the most commonly used antibiotics. Tetracyclines are not recommended in people younger than 10 years of age due to the risk of permanent changes in the color of the teeth. Rifampicin associated to clindamycin can be used in the pediatric group.⁶² Isotretinoin was also frequently described in these series, despite not being the first choice due to the limited effect described in adults.63 Regardless of the presence or absence of premature adrenarche in the endocrinological evaluation, antiandrogens such as finasteride (1 to 5mg/day) have been shown to be effective in refractory HS in children.^{64,65} Two case series (3 and 5 children) showed efficacy and achievement of remission for variable periods of 5 to 24 months, with few adverse events. Due to the risk of feminization of the fetus, its use is recommended in cases refractory to topical and oral antibiotics, before considering biologic or surgical

treatment. Finally, the use of botulinum toxin was reported with an initial satisfactory result but recurrence after 6 months.⁶⁶

Women of childbearing age

Case series comparing women using antiandrogen medications (conjugated contraceptive with cyproterone; spironolactone; spironolactone and cyproterone; 29 cases) *versus* oral antibiotics (tetracyclines, trimethoprim/sulfamethoxazole; 23 cases) showed a higher response rate in the first group (55%) when compared to the second group (26%).⁶⁷ Antiandrogen strategy in women is an interesting option with level of evidence C and can be indicated for those who fail antibiotic treatments. The ideal antiandrogen regimen is controversial, with no differences in HS responses identified with ethynilestradiol combined with cyproterone or with norgestrel.⁶⁸

Isotretinoin was evaluated in 7 different studies with levels of evidence B and C, and the collective of patients in these studies showed lack of efficacy in 64%. Despite the high percentage of responders in studies with acitretin, with levels of evidence B and C, it is not appropriate to women of childbearing age, and in this situation the choice of isotretinoin over acitretin is justified.⁶⁹

The use of systemic steroids is based in a study with hydrocortisone published in 1958. The disease responds to high daily doses of prednisone 0.5-0.7 mg/kg/day, with recurrence after dose reduction. Therefore, systemic steroids are indicated essentially for flares, for short periods of time. However, a publication of a small case series shows that low daily doses for limited periods can be useful for refractory cases, associated to other medications.

Metformin was studied in a case series with 25 individuals (22 of those were females) with a previous history of antibiotic use and 11 of them using isotretinoin. In doses of up to 1.5g/day, 19 of these patients showed responses (DLQI and/or Sartorius) in 12 to 24 weeks.⁷¹

Zinc gluconate is an option for the maintenance treatment in Hurley stages I and II, in a 90 mg dose divided into three doses. The possible impairment in iron and copper absorption and gastrointestinal bleeding can limit its long-term use.^{3,72}

Dapsone was evaluated in 3 different studies with level of evidence C, demonstrating a significant response in 35%, moderate in 21% and absent in 44%, suggesting its use in patients who fail first- or second-line systemic treamtents.⁶⁹

Data for methotrexate and ciclosporin are not robust and these drugs should be considered as third-line of association for long-term inflammation control.

Non-childbearing age women and men

Tetracycline 500mg twice daily led to a reduction of approximately 30% in disease severity but showed no benefits when compared to 1% topical clindamycin.⁴⁸ The association of clindamycin and rifampicin was tested in 3 case series studies with the 300mg dose of clindamycin and 600mg of rifampicin daily for 10 weeks, demonstrating global, pain and Sartorius score improvement. ⁷³⁻⁷⁵

A recent study demonstrated that the association of clindamycin (600 to 1800mg, according to the weight) and ofloxacin (200 to 400mg) for a mean observation period of 4.3 months led to comparable results to the association of rifampicin and clindamycin.

Sixty-five patients were treated and 33.8% had complete response and 24.6% partial response, regardless on the initial Hurley stage.⁷⁶

The combination of minocycline 100mg daily for 6 months and colchicine 0.5mg twice daily for 9 months was also reported in a pilot study with 20 patients. More than 90% of patients had a PGA (Physician Global Assessment) between good and excellent for up to 9 months of observation.⁷⁷

There are reports of improvement in retrospective studies with few patients with dapsone in doses between 25-200mg/day for at least 3 months, with fast recurrence after discontinuation.^{78,79}

The use of isotretinoin for the treatment of HS is questionable. Studies show that 64.4% of patients are non-responders and those who respond have mild forms (Hurley I). Dose can range between 0.5-1.2mg/Kg/day.⁸⁰⁻⁸⁵ Acitretin shows higher response rates as demonstrated in a study where 21 out of 32 patients (65.6%) had a marked improvement, 8 patients (25%) had a moderate improvement and 3 patients (9.4%) did not respond to the treatment with daily doses of 0.25-0.88mg/kg for 3 to 12 months.⁸⁶⁻⁹²

STEP 3

Biologic treatment

Biologic drugs have a well-established role for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease. The first reported case of hidradenitis suppurativa responsive to treatment with infliximab in a patient with Chron's disease was in 2001. This publication revolutionized the perception of the disease and subsequent studies lead to a change in the paradigm of the pathogenesis and treatment of hidradenitis. TNF-alpha (tumor necrosis factor alpha) is a pro-inflammatory cytokine with a central role in the pathogenesis of hidradenitis suppurativa, as well as IL-1 and IL-17. Also, IL-6, IL-12 and IL-23 have a relevant role.

Cytokines became an important target for inflammation control, integrating the armamentarium employed in the management of hidradenitis suppurativa, what was acknowledged in consensuses, reviews and guidelines for the management of the disease already published in many countries. 99-106

TNF-alpha blockers, including adalimumab, infliximab and etanercept, were the first biologics studied for the treatment of hidradenitis suppurativa. Among them, adalimumab is the one with more complete studies, with better level of evidence (1B) for the treatment of hidradenitis suppurativa.

ADALIMUMAB

Adalimumab is a fully humanized monoclonal antibody proteins that target soluble and transmembrane TNF-alpha. $^{\rm 93}$

Adalimumab is the only approved medication that is indicated for the treatment of hidradenitis suppurativa. ¹⁰⁷⁻¹⁰⁹ The medication is approved for this indication by the European Medicine Agency and the Food and Drug Administration.

Phase 3 studies, known as PIONEER I and PIONEER II, demonstrated the efficacy of adalimumab for the treatment of hidradenitis suppurativa, superior to placebo. The primary outcome was HiSCR (Hidradenitis Suppurativa Clinical Response) at week 12.

In PIONEER I, 307 patients were selected (154 for placebo;

153 for adalimumab) and in PIONEER II, 326 (163 for placebo; 163 for adalimumab). The rate of HiSCR achievement at week 12 was significantly higher for patients randomized in the weekly adalimumab group (41.8% vs. 26.0% in PIONEER I, p=0.003; 58.9% vs. 27.6% in PIONEER II, p<0.001). 109

At week 36 (period B), a higher rate of HiSCR achievement was observed for all patients that received weekly adalimumab in periods A and B (43.8% in PIONEER I and 47.1% in PIONEER II) compared to patients that received weekly adalimumab in period A and were re-randomized for application every 2 weeks (31.3% in PIONEER I and 41.5% in PIONEER II) or placebo (26.5% in PIONEER I and 41.5% in PIONEER II) in period B.¹⁰⁹

Adalimumab was also effective for improving the quality of life of patients with HS. HiSCR rates were maintained long-term and the safety profile in moderate to severe HS patients was similar to that reported for the drug in other indications. ¹⁰⁹ A recent study demonstrated that the ratio of patients with reduced infectious events related to the treatment was higher when compared to placebo. ¹¹⁰

The need for higher induction and maintenance doses to achieve better disease control in comparison to the doses used in rheumatoid arthritis, psoriasis and Crohn's disease is related to a higher inflammatory burden of hidradenitis suppurativa in relation to those diseases.⁵⁴

Adalimumab dosing for the treatment of hidradenitis suppurativa was established with the PIONEER II study and is of 160mg at day 1, 80mg at day 14 and 40mg weekly from day 29. The treatment is indicated for a period determined by the treating physician. Once the inflammation is under control, the areas with residual activity or scarring can be excised. Treatment maintenance with adalimumab contributes to reduce recurrences.¹¹¹

INFLIXIMAB

It is a chimeric antibody formed by human and murine proteins that targets soluble and transmembrane TNF-alpha. 93 After the initial publication of 2001, many case reports and small series confirmed the value of infliximab for the treatment of hidradenitis suppurativa. Improvement of multiple parameters was demonstrated but appropriate evaluation scales were not used. A placebo controlled, randomized, double-blind clinical trial on the use of infliximab in HS included 38 patients who received infliximab (5mg/kg in weeks 0, 2 and 6 and every 8 weeks thereafter) or placebo; after 8 weeks an open-label phase followed, in which those receiving placebo could receive the drug. $^{\!\!\!\!112}$ It was observed that 26% of the patients in the group receiving the treatment had a 50% or more improvement when compared to 5% in the placebo group. Moreover, scores like DLQI (Dermatology Quality of Life Index), pain and PGA demonstrated an improvement in relation to baseline when compared to the placebo group. Monotherapy with infliximab was well tolerated and a higher number of adverse events occurred in the placebo group.112

As well as with adalimumab, better results are achieved with doses of 5mg/Kg every month after the induction phase with 5mg/Kg at the starting week, week 2 and week $6.^{113}$ Methotrexa-

te can be added to improve efficacy of the treatment with infliximab, particularly in patients with spondyloarthropathies associated to HS 93

ETANERCEPT

It is a fully human fusion protein formed by the TNF-alpha receptor and by the protein component of the immunoglobulin G1 receptor. This protein only binds to soluble TNF-alpha and not to transmembrane. 93

The first publications pointed towards a benefit of the use of etanercept in the treatment of HS.¹¹⁴⁻¹¹⁶ Subsequently, a study did not show benefits with the use of etanercept 50mg weekly, discouraging subsequent protocols. The studies involved few patients and non-validated evaluation scales, hindering possible conclusions about its employment in the disease.

USTEKINUMAB

Ustekinumab is a human monoclonal antibody with high affinity for the p40 subunit of IL-12 and IL-23. IL12/23 pathway is implicated in the pathogenesis of hidradenitis suppurativa and, besides, polymorphisms in IL-12 beta-1 receptor influence the clinical picure.

Ustekinumab was successful for the treatment of hidradenitis suppurativa reported in isolated cases. [11,117-120] Blok *et al* reported the use of ustekinumab in 17 patients with moderate to severe HS in a prospective, open-label study with validated outcome measures. Twelve patients completed the study; 82% of patients showed moderate to significant results. The mean improvement in the modified Sartorius score was of 46.3% and 7 patients (41%) had a significant reduction in DLQI. The medication was administered subcutaneously, in a 45mg dose or 90mg if the weight was over 100kg. The authors noticed that the dose administered was the one approved for psoriasis and that higher doses might be necessary for the treatment of hidradenitis suppurativa, as in Crohn's disease. [21]

ANAKINRA AND CANAKINUMAB

Anakinra is a recombinant antagonist of IL-1-alpha receptor that competitively binds to IL-1 receptors and prevents the interaction of IL-1 accessory protein with the receptor, resulting in signal blockage.⁹³

IL-1 pathway blockers have been used in the treatment of HS, especially in syndromic forms. Anakinra is not available in Brazil. Canakinumab, a IL-1-beta inhibitor, was successfully used for the treatment of HS in sparse case reports. 122-124

SECUKINUMAB

Secukinumab is an anti-IL-17A monoclonal antibody that binds to that cytokine preventing its interaction with receptors and inhibiting the inflammatory cascade. Studies demonstrated the importance of this pathway in the pathogenesis of HS.¹²⁵ An extensive and severe case, resistant to multiple treatments was treated with secukinumab and showed a fast and significant response, demonstrating that blockage of IL-17A has a role in the management of HS.¹²⁶

APREMILAST

Apremilast, an inhibitor of phosphodiesterase-4, is a small oral molecule, that showed satisfactory results for the treatment of HS in a small case series and is a subject for protocols for this indication.⁹³

BIOLOGICS COMBINED TO OTHER THERAPEUTIC MODALITIES

Biologic drugs can be used in association to other medications such as antibiotic, hormonal therapies, surgical treatments of cutaneous lesions, etc.¹⁰⁹

The combination of radical resection with treatment with targeted biologic therapy was evaluated for hidradenitis suppurativa, comparing disease recurrence and progression. The medications used were infliximab and ustekinumab, when the former was not available. Treatment was commenced after surgery, when there were no complications and carried out for a minimum period of 6 months. The authors demonstrated lower recurrence and progression rates in the group treated with biologics for at least 6 months. The protective effect of biologics reduced over time after discontinuation of treatment. Another study evaluated 68 cases in which biologic treatment was associated to surgery, concluding that the combination of both modalities led to a faster decline in disease acitivity.

TREATMENT OF HIDRADENITIS SUPPURATIVA ASSOCIATED TO OTHER INFLAMMATORY CONDITIONS

Targeted therapy with biologic drugs can be indicated in cases of hidradenitis suppurativa where there is association with other inflammatory diseases such as pyoderma gangrenosum, severe acne, arthritis, osteitis, spondyloarthropathies, psoriasis, follicular occlusion triad - as the association of hidradenitis suppurativa, acne conglobata, dissecting cellulitis is known (called tetrad when pilonidal sinus is present) and inflammatory bowel disease. Biologic drugs can be indicated for the control of one of the conditions even if the others are under control, prioritizing the treatment of the patient as a whole and not of the individual manifestations.

Manifestations known as paradoxical can subsequently develop in patients with conditions being treated by biologics and changing the biologic drug or associating it to other treatments might be necessary to fully control the clinical manifestations.

RECOMMENDATIONS FOR THE TREATMENT OF HIDRADENITIS SUPPURATIVA ACCORDING TO THE LEVEL OF EVIDENCE, GRADE OF RECOMMENDATION AND DEGREE OF AGREEMENT AMONG SPECIALISTS

The topics discussed and voted by the experts are indicated in charts 2 and 3, according to level of evidence and degree of recommendation.

It was a consensus among the specialists that measures such as weight loss, smoking cessation, hair removal and local antisepsis should be recommended, with a concordance of 100%.

Topical treatment for isolated and superficial lesions is a possibility, and topical 1% clindamycin has the best evidence and is incorporated in international guidelines as first line. The use of fusidic acid and 15% resorcinol is justified in the literature but there is no evidence of the benefit of the use of other topical treatment mo-

dalities like benzoyl peroxide and retinoids. The 75% concordance among the specialists was for the use of clindamycin, fusidic acid and resorcinol. It is important to emphasize that HS lesions have a self-limited course.

The rational use of topical antibiotic is a growing concern due to the risk of bacterial resistance. ¹²⁷⁻¹²⁹ The recommendation is to use it for a limited time and avoid repeating it. The association with other topicals such as benzoyl peroxide or replacement with resorcinol are a good strategy to minimize the risk.

Regarding intralesional therapies, the concordance among the specialists was of 100% for the use of triamcinolone acetonide in the case of localized nodules and abscesses with inflammatory signs.

Sulfa and tetracycline substances were indicated as first choice. Among those, the medications trimethoprim/sulfamethoxazole and tetracycline were the most voted.

The order of specialist preference for the drugs used in the treatment of HS for adult men and women of non-childbearing age was as follows: sulfas/tetracyclines, acitretin, clindamycin plus rifampicin, zinc, metformin, finasteride, isotretinoin and systemic steroid. For women of childbearing age, the choices according to the order of preference were: sulfas, tetracyclines, oral contraceptive, systemic steroid, metformin, isotretinoin, clindamycin plus rifampicin, zinc and finasteride. The use of acitretin demands caution due to the risk of teratogenesis. For children younger than 12 years, the specialists' order of preference was: sulfas, isotretinoin, acitretin, finasteride, zinc, systemic steroid and clindamycin plus rifampicin.

To confirm if there was any difference in the specialists' preference regarding the type of medication to be used, the Friedman test was used and the level of significance adopted was of 5%. The results demonstrated that preferences are not similar among specialists.

Therefore, the concordance regarding the use of antibiotics such as sulfas and tetracyclines in the initial approach of moderate to severe HS was of 100% among the specialists.

There must be caution with the use of rifampicin. ¹³⁰ In Brazil and in countries where there is a high prevalence of tuberculosis and Hansen's disease, its use should be discussed with local epidemiological surveillance authorities. These infectious diseases should be screened before starting the treatment. Rifampicin is a first-line drug for the treatment of tuberculosis. The incidence of tuberculosis cases resistant to polychemotherapy has increased worldwide and particularly in countries where the disease has a high prevalence, according to an alert from the World Health Organization (WHO). The association of other antibiotic regimens such as clindamycin and ofloxacin can have similar efficacy. ⁷⁶

Systemic treatment with clindamycin plus ofloxacin can be indicated in cases of moderate to severe HS as second-line antibiotic therapy. There was an 87.5% concordance among specialists for this statement.

The course of antibiotic therapy should be long, for at least 10 to 12 weeks and with optimized doses.

It can be associated with or followed by other medications with an anti-inflammatory or antiandrogen effect. Other immunomodulators such as dapsone, for example, can be considered as

Intervention	Level of evidence/Grade of	Intervention	Level of evidence/Grade of
	recommendation		recommendation
Weight Loss	II/B	Clindamycin	II/B
Smoking Cessation	II/B	Erythromycin	V/D
Local Antiseptics	IV/C	Fusidic acid	IV/C
Hair Removal	I/A	Gentamicin	IV/C
Dressings	II/B	Clindamycin + Benzoyl peroxide	IV/D
		Resorcinol	III/C
		Topical Retinoid	IV/C
		Intralesional Steroid	IV/D
		Botulinum Toxin	IV/D

Chart 3: Systemic treatments for HS according to the level of evidence and grade of recommendation based on the literature			
	Intervention	Level of evidence/Grade of recommendation	
Oral antibiotics			
	Trimethoprim/sulfamethoxazole	IV/D	
	Tetracyclines (tetracycline)	II/B	
	Clindamycin + rifampicin	III/C	
	Clindamycin + ofloxacin	III/C	
Oral retinoids			
	Acitretin	II/C	
	Isotretinoin	IV/D	
Antiandrogens			
	Metformin	II/B	
	Finasteride	III/C	
	Ethynilestradiol	III/C	
Anti-inflammatories and immunosuppressants			
	Systemic steroid	IV/D	
	Dapsone	III/C	
	Zinc	III/C	
Biologics			
-	Adalimumab	I/A	
	Infliximab	II/B	
	Etanercept	III/C	
	Anakinra	III/C	
	Canakinumab	IV/D	
	Ustekinumab	III/D	
	Secukinumab	IV/D	
	Apremilast	IV/D	
	_		

maintenance therapy for cases with frequent flares, avoiding or delaying the repeated use of antibiotics. Systemic steroids can initially contribute to reduce the inflammation but its prolonged use should be avoided due to adverse events and the risk of disease rebound.

Oral retinoids can be an option for the forms associated with acne or clinical forms folliculitis-type. Acitretin was shown to be more effective than isotretinoin but it has restrictions in women of childbearing age.

Patients with moderate to severe hidradenitis suppurativa can be treated with anti-TNF-alpha biologic drugs. These medications can be used in association with surgical treatment of cutaneous lesions. In the forms exceptionally severe associated to other conditions, biologic drugs can be indicated for the control of the manifestations even if the others are under control, prioritizing the treatment of the patient as a whole and not of the manifestations individually.

For all these statements, the concordance among the specialists was of 87.5% and there was consensus to indicate anti-TNF-alpha biologic drugs for patients with moderate to severe hidradenitis suppurativa. Biologics are alternatives for recurrent cases that do not respond or respond partially to the first interventions.

SURGICAL TREATMENT

Cases of moderate to severe HS with tunnels and scars typi-

cal of Hurley stages II and III are indications for surgical treatment. When there is considerable tissue damage, the clinical treatment cannot revert the tissue changes, that becomes a site of recurrent inflammation and secondary infection.^{131,132} Biofilms can form inside the tunnels, which are sometimes epithelialized in their interior, maintaining the inflammatory features of the disease. A literature review showed that biofilms are implicated in many dermatological conditions, prevent wound healing and cause recurrent infections.¹³³

Surgery for HS is a challenge for the dermatological surgeon since there are controversies regarding the appropriate technique, extension and reconstruction of the area excised. It is important that the inflammatory process be minimum to demarcate the limits of the lesions and improve surgical and postoperative conditions.¹³²

In the acute phases, the procedures should be restricted to abscess incision/drainage for symptoms relief. Deroofing, a technique described by Mullins in 1959, can be performed for localized disease and consists in the removal of the roof of the tunnel using scissors, blade, electrosurgery or $\rm CO_2$ laser, directed by a probe, leaving the clean wound bed to heal for secondary intention. ¹³² Van der Zee *et al*, in 2010, showed that 83% of 88 Hurley I and II lesions submitted to deroofing had no recurrence in 34 months of follow-up. It is a simple technique that allows for speedy recovery and can be performed in the outpatient setting. ¹³⁴

The risk of recurrence is higher with partial simple excision than with wide excision. ¹³⁵ Surgical planning should be evaluated case by case, and it is not always possible to remove the whole affected tissue in one single step. Tumescent anesthesia, sedation or general anesthesia should be considered for wide excisions.

In chronic cases, wide excision of the affected area yields better results and lower chances of local recurrence. Removal of all tissues affected should be performed including dermis and subcutaneous tissue and sometimes including the underlying fascia, down to where the lesions extend, besides 1 to 2cm lateral margins. If there are doubts regarding the extension of the lesions, ultrasound and/or nuclear magnetic resonance can contribute to the recognition and demarcation of the affected area. ¹³⁶⁻¹³⁸

Reconstruction is the real challenge and the rule of simplification also applies to HS surgery. Therefore, secondary intention healing, primary closure, grafts and flaps are considered, in this order. Secondary intention healing has advantages because it reduces the time for surgery and provides good cosmetic and functional results, even though the recovery time is longer. Vacuum therapy (V.A.C) and special dressings contribute to a quicker resolution of the surgical wound. However, in certain situations, coverage is important to avoid exposure of important structures such as nerves and vessels, reduce the risk for secondary infections, prevent retractions and reduce the time for healing in the postoperative period. ¹³²

Data are variable regarding the risk of recurrence after surgery, according to the anatomical sites treated and the techniques used. Weight and smoking seem to be the main risk factors for local recurrence.¹³⁹

A retrospective study evaluated 84 patients after wide excision, with a total of 253 procedures and mean follow-up of 36 months. Recurrence was observed in 37% in 6 months on average (genital region was the most susceptible), total remission in 49% and

natural progression of the disease in 13%. Most patients reported a high level of satisfaction with the results obtained. ¹⁴⁰ A German study retrospectively analyzed Hurley III patients who were submitted to wide excisions and observed that 95% still had life restrictions related to the disease, although 80% of them were satisfied with the results. This shows that treatment should be combined and there is room for clinical approach before and after surgery. ¹⁴¹

Surgery during pharmacological treatment is another controversial matter, particularly considering biologic drugs. Patients who underwent surgery while on a biologic drug had better disease control than those who only had medical treatment in a study with 68 cases of moderate to severe ${\rm HS}^{.142}$

The use of laser technologies has been appreciated for ablation and destruction of chronic lesions. Carbon dioxide laser (CO₂) can be used for vaporization and excision. Nodules, abscesses and tunnels can be targeted, leaving healthy tissue in between the lesions treated. This way, the technique can spare the surrounding healthy tissue, with appropriate hemostasis and allow for speedy healing. The reports of the studies show less pain and a more comfortable postoperative period than with traditional surgery. 143-146 Intense pulsed light can provide favorable results even in Hurley II and III cases according to case series published, even though it has superficial penetration. 147,148 Nd:YAG 1064-nm laser can be useful for hair removal, treatment of superficial lesions or associated to other modalities in moderate to severe cases. The study by Tierney et al, prospective, randomized, with 22 patients, consisted of three monthly sessions of the therapy on half of the patients' body, while the other half was only treated with topical antibiotic, demonstrating that the result of the association was considerably better.44

FINAL CONSIDERATIONS

HS is considered to be one of the diseases that impairs the quality of life of affected individuals the most. Current knowledge on its ethiopathogenesis has grown considerably and has confirmed its immune-mediated background. Treatment of the disease in early phases where there is pre-clinical inflammation without structural damage can avoid or reduce the devastating progression to fistulas and scarring, which will require surgical treatment. Thus, early diagnosis, interventions on risk factors such as treating obesity, metabolic and hormonal disturbances and smoking cessation measures when the first signs arise are factors that can interfere with the course and severity of the disease.²²

The inflammation phase that precedes tissue destruction represents the window of opportunity to adequately approach the disease. Treatment with antibiotics and immunosuppressants can contribute to a better systemic control of the inflammation, its repercussion in other organs and its complications.⁵⁴

HS patients should be screened annually due to the high prevalence of associated diseases and the higher risk of cardiovascular disease. Obesity, diabetes, hypertension, metabolic syndrome, besides inflammatory bowel disease, joint disorders, anxiety and depression, smoking and alcoholism are important conditions that should be investigated.²²

Clinical and surgical care should be constant since in acute phases, drainage and minor excisions can be necessary and in ad-

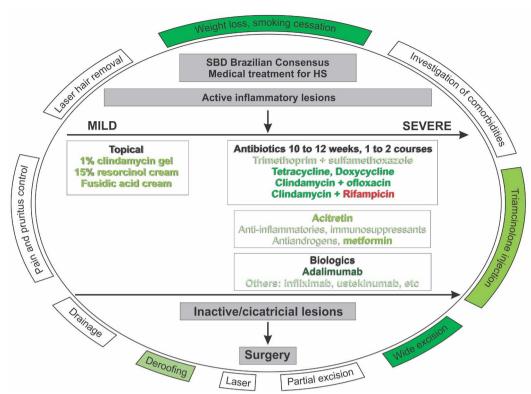


FIGURE 1: Recommendation for treatment of suppurative hidradenitis according to the Brazilian HS Consensus. Interventions in darker tones have higher grades of recommendation, those in red should be considered with caution. Surgical interventions and general measures should be considered throughout patient follow-up. Recommended doses for medications can be adjusted according to medical indication (trimethoprim + sulfamethoxazole 160mg/800mg bid; tetracycline 500mg bid (up to 2g/day), doxycycline 100 to 200mg/day, clindamycin 600 to 1800mg/day + ofloxacin 200 to 400mg bid, clindamycin 300mg qid + rifampicin 600mg/day, adalimumab subcutaneously 160mg D0, 80mg D14, 40mg/week

vanced phases, established fistulas with frequent suppuration and scarring, that are considered static lesions, require wide excisions. In this sense, multidisciplinary care should be encouraged.¹⁴²

The use of biologics drugs was shown to be effective and safe in HS, indicated for moderate to severe cases that failed conventional treatment. An European consensus, based on a systematic review of the literature and voted by the Delphi system among experts, suggests that the immunobiological treatment should be

maintained for at least one year if the patient is a good responder, but if there is no improvement of at least 25% in HiSCR in the first twelve weeks, this should be reconsidered. ⁹⁹

The aim of this consensus is to guide the dermatologist in the approach of the patients with HS in the Brazilian reality, and the authors are open to reevaluation and updating, besides the evaluation of its impact in the dermatology Community (Figure 1). \square

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How to cite this article: Magalhães RF, Rivitti-Machado MC, Duarte GV, Souto R, Nunes DH, Chaves M, Hirata SH, Ramos AMC. Consensus on the treatment of hidradenitis suppurativa – Brazilian Society of Dermatology. An Bras Dermatol. 2019;94(2 Suppl 1):S7-19.