National Consensus

HIDRADENITIS SUPPURATIVA

Published by the Sociedad Argentina de Dermatología [Argentine Society of Dermatology] – Year 1- No. 1 – November 2019
Location of editing: Ciudad Autónoma de Buenos Aires, Argentina

2019 Treatment Guideline

ICD 10: L73.2
ICD 11: ED92.0
Synonym: acne inversa

Autoinflammatory Disease and Hidradenitis Suppurativa Work Group
of the Argentine Society of Dermatology

SOCIEDAD ARGENTINA DE DERMATOLOGÍA

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1. INTRODUCTION

The objective of treatment guidelines is to facilitate decision-making at the time of prescribing a treatment focusing on providing patients with the adequate therapy. This comes from the equations which assess efficacy, safety and risk/benefit, to achieve cure when possible or to provide a satisfactory quality of life to patients with a chronic condition.

Guidelines are not a dogma, but a picture of a moment, based on knowledge and evidence, which translates into recommendations. For this reason, they should be updated on an ongoing basis according to scientific breakthroughs, and both expertise and evidence should be the tools to shape them. Thus, guidelines are scientific documents based on evidence and levels of expert recommendations.

Once evidence is acquired and ranked, and recommendations subsequently made, it is necessary to standardize the process of preparing guidelines. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach is a system used to rate the quality of evidence and the strength of recommendations. By means of this approach, used for the present document, the quality of evidence is rated as high or low depending on whether it comes from investigational or observational studies, and, subsequently, according to factors such as the risk/benefit balance, values and preferences of patients and healthcare providers and the use of resources, leading to the high, moderate, low or very low evidence.

Guidelines should not address health economics-related financial or political considerations in its main body. What they should consider are regional epidemiological issues which may interfere with or change response to therapy. However, consideration may be given to a booklet to be attached establishing limiting economic situations and considerations which facilitate the course to follow to overcome those barriers. The preparation of a guideline based on economic concepts or a guideline based on indigence may be considered, but it is not the objective of this project.

Such guidelines are addressed to dermatologists, internal medicine physicians, gastroenterologists, medical imaging technicians, infectologists, surgeons and healthcare professionals qualified for the management of hidradenitis suppurativa. They include the process of diagnosis, classification and subsequent therapy to be instituted.

2. PREMISES

Hidradenitis suppurativa (HS) is a disease which not many years ago had no specific therapy and prescriptions were made at the discretion of and according to the experience of the treating physician. However, from recent studies which have re-interpreted the disease and improved the understanding of its physiopathology, now there are indications based on pivotal studies which qualify levels of evidence and levels of recommendation. Thus, there is a new therapeutic target represented by proinflammatory cytokines such as tumor necrosis factor (TNF) and different interleukines (IL).

In view of this new knowledge, biologic agents appear as a new therapeutic tool. Infliximab and adalimumab (anti-TNF) are in the cutting-edge of therapeutic trials. Thus, the first specific therapy approved by the Food and Drug Administration (FDA), the European Medicine Agency (EMA), and, in Argentina, the National Administration of Drugs, Food and Medical Technology (ANMAT – *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*) is introduced: adalimumab. It is a monoclonal antibody approved for the treatment of HS, both in adults and adolescents (>30 kg weight). It is the only first-line medical systemic treatment approved for HS, IB evidence category and recommendation A level.

3. BACKGROUND ON HIDRADENITIS SUPPURATIVA

3.a. Definitions

Hidradenitis suppurativa:

Hidradenitis suppurativa (HS) is a chronic systemic autoinflammatory, recurrent, debilitating and potentially disabling disease, which presents in the hair follicle in apocrine gland-rich areas of the body.

Window of opportunity:

Period of time during which efforts aimed at controlling inflammatory activity may be most useful. It is found in the early stages of disease, prior to the initiation of sequelae, which later lead to irreversible damage. It is considered that immunomodulatory therapy may reduce tissue damage extent and disrupt the natural history of disease. Therefore, it is critical to make an early diagnosis to institute the adequate treatment within the *window of opportunity* and thus provide patients with a good quality of life.

In the presence of fistulas and scarring, considered as sequelar evolutionary lesions, therapy should be combined. On the one hand, it should aim at reducing inflammation by cooling active lesions, and, on the other hand, performing surgical procedures to remove refractory fistulas and scars.

3.b. Epidemiology

It affects all ethnic groups, with a global prevalence estimated to be 1%, based on European trials[1]. There are no published data from Latin American countries. A National Register was created in Argentina which included patients for the period 2017-2018 reaching the number of 253 patients[2]. Women are three to five times more likely to have HS than males. The incidence in females is higher between the ages of 20 to 40 years, with an inverse relation after the age of 45[2-4]. After the age of 55, a significantly reduced prevalence is seen in both sexes[5]. It may start at puberty and 2-3% of the cases before the age of 11 years[6,7].

3.c. Physiopathogenesis

Hair follicle has a critical role in the development of the disease, as evidenced by the presence of keratin plugs as the primary event and apocrine gland inflammation as secondary event. Epidermal hyperplasia, with subsequent follicular occlusion, results in the enlargement of the follicle, with the onset of the first inflammatory events (chemotaxis of inflammatory cells and release of cytokines). Soon after, follicular rupture is produced with spilling of its content (bacteria, sebum, keratin, hairy fragments) into the dermis, leading to a late inflammatory process with formation of nodules and abscesses and subsequent onset of sinus tracts and fistulas.

This process occurs in a predisposing setting, determined by genetic changes, environmental factors and different changes in the microbial flora, resulting in the activation of innate immunity which causes an overexpressed and sustained inflammatory response[8]. Various cytokines take part in the process: IL-1β, IL-10, IL-17, IL-23 and TNF-α[9,10] (Figure 1). Inflammasome activation was also described which produces high molecular weight keratins.

The role of bacterial microbiome, as shown through biopsy and culture, is not clearly known, and neither that of the biofilm which lines fistulas. However, they may be related to the onset and persistence of the disease resulting in the persistence of the inflammatory cascade[11,12].

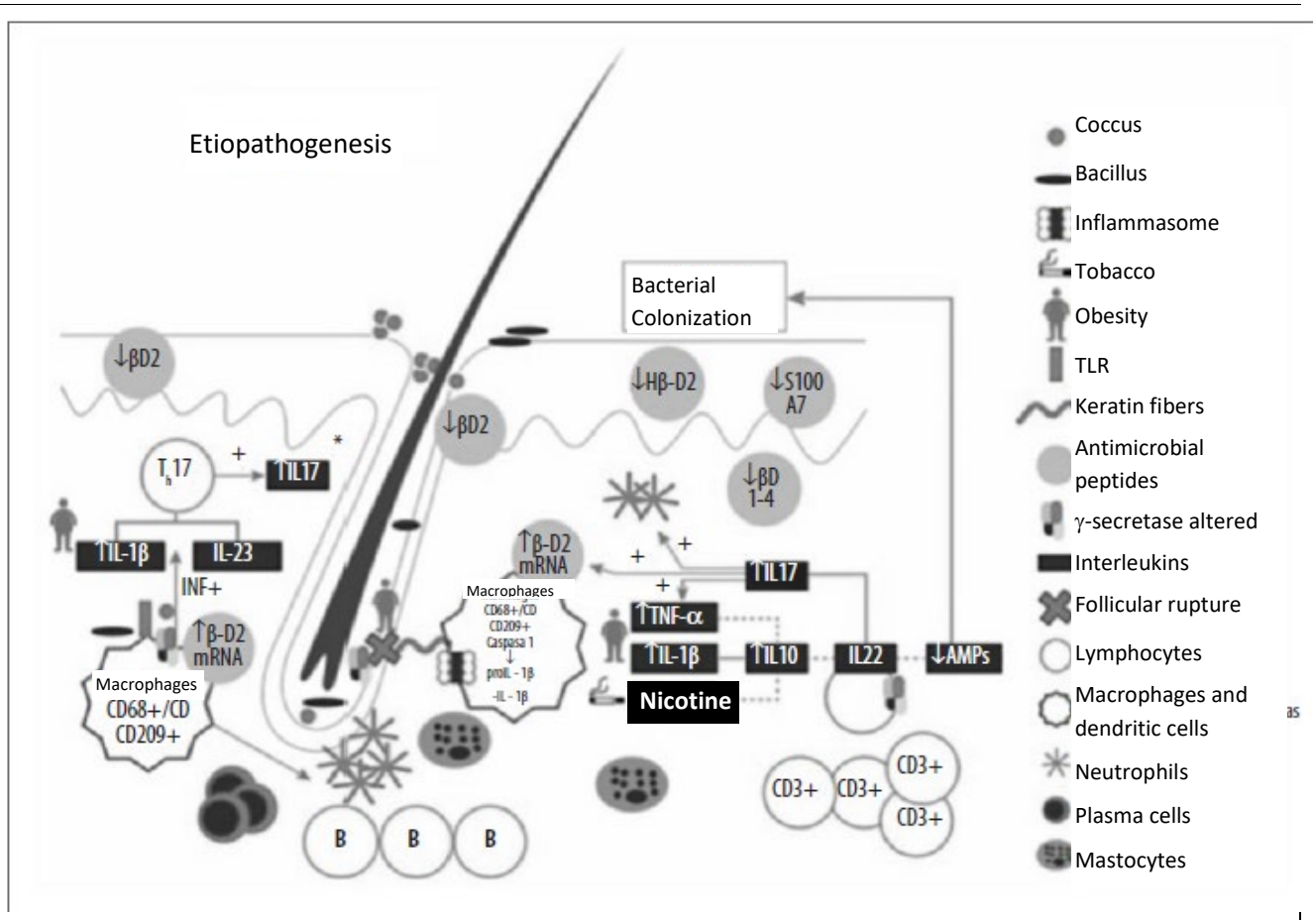

Figure 1: Physiopathogenesis[11]

3.d. Risk factors[2,7,13,14]

Genetics, obesity and smoking are considered determining factors; friction is a factor also to be taken into account.

Genetics: its contribution is supposed to be of 5%. Thirty-thirty-three percent of the patients with HS have a family history. The Notch pathway with gamma-secretase dysregulation and mutations in the genes *PSEN1* and *PSENEN, NCSTN* and *PSTPIP1* are changes studied in this disease.

Obesity: There is a strong association between HS severity and body mass index (BMI). Rubbing and friction in areas of flexion have also been associated with a mechanical stress mechanism.

Association of HS to BMI by sex:

- Males with overweight 70%/Obese males 26%
- Females with overweight 69%/Obese females 24%

Smoking: Probability of suffering HS is 9,4 times higher in active smokers (89%) than in non-smokers or former smokers (11%). Active smoking is associated with more severe forms of the disease.

Other factors associated with severity: male sex; longer time course of disease; axillary, mammary and perianal involvement and high CRP levels[15].

3.e. Genetics and syndromic associations[13,16]

There is a familial association in one third of the patients. Therefore, it is evident that genetic factors play a key role in its physiopathogenesis. These factors may be grouped in: genes, associated syndromes and epigenetic phenomena.

- **Genes**: cases with familial association have been published, and in recent reports several mutations in the following genes have been identified: *PSENEN, PSEN1, NCSTN, PSTRIP1, POFUT1*, etc
- **Associated syndromes**: multiple syndromes associated with HS have been described. There are familial cases of several generations associated with mutations in the ***NCSTN*** gene, studied in a Chinese population of the Han ethnia, and, in the ***PASH*** syndrome associated with HS. Mutations in the ***PSENEN*** gene, present in some HS cases, have been associated with clinical symptoms of the Dowling-Degos disease and comedonic syndromes. Mutations in the ***PSTRIP1*** gene have been identified in some cases of HS associated with the *PASH, PAPA, PAPASH* and pyoderma gangrenosum syndromes.
- **Epigenetic phenomena**: there are reports of epigenetic phenomena, such as global alteration of 5-hydroximethylation, which could explain, in part, the etiopathogenesis of HS.

3.f. Comorbidities[16]

HS may be associated with concomitant or secondary diseases, such as obesity, metabolic syndrome, intestinal inflammatory disease, spondyloarthritis, mental disease, renal disease, pyoderma gangrenosum, Behcet disease, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, Dowling-Degos disease, pachyonychia congenita, KID (keratitis, ichthyosis, deafness) syndrome, PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) syndrome, PASH (pyoderma gangrenosum, acne, hidradenitis suppurativa) syndrome, PAPASH (pyogenic arthritis, acne, pyoderma

gangrenosum, hidradenitis suppurativa) syndrome, Down syndrome and follicular occlusion tetrad syndrome (acne conglobata, hidradenitis suppurativa, dissecting folliculitis, pilonidal sinus)[17]. The Down syndrome, polycystic ovary syndrome, thyroid disorders and premature menarche are usually associated with pediatric HS[18].

Several studies support the negative effect of obesity on HS progression and severity[19-25]. In a study conducted in 846 patients with HS, 36.2% had normal weight, 31.5% were overweight and 32.3% were obese[19]. In another study which included 249 patients who underwent bariatric surgery, 45 (18.1%) had HS; of these, 48.6% experienced no symptoms since weight loss, 20% had mild activity in the sites involved, 20% experienced no changes and 11.4% experienced increased activity of disease[20].

As to BMI, a multicenter study assessed 246 patients with BMI < 25 as compared to 205 patients with BMI > 35. Patients with the highest BMI experienced a more severe disease (Hurley, physician global assessment, number of affected areas and severity informed by the patient). In patients with BMI < 25, with increasing BMI, severity informed by the patient also increased significantly[21]. Chronic systemic inflammation experienced by patients with HS is more frequently associated with metabolic syndrome. Sabat et al observed a higher prevalence of metabolic syndrome, as well as of most of its criteria (abdominal obesity, hyperglycemia, hypertriglyceridemia, hypo-cholesterol HDL) as compared to a healthy control group. It is worthwhile commenting that the most affected group is the population of HS patients aged less than 35 years[22].

Autoinflammatory diseases most frequently associated are intestinal inflammatory disease, 1.2%-23% (17% Crohn's disease and 14% ulcerative colitis), and asymmetric spondyloarthritis HLA-B27-negative, 0.7-1%. Arthritis usually occurs after HS development and prevalence is unknown. There are very different rheumatic diseases, such as axial or peripheral arthritis, dactylitis, enthesopathies, unilateral sacroiliitis and anterior chest wall involvement. Indirect inflammation markers increase, and erosions, osteoporosis, sacroiliitis and syndesmophytes can be seen on images. It was observed that theclinical improvement of HS is associated with subsequent improvement of joint symptoms.[23,24].

As to the association with other polygenic autoinflammatory diseases such as PAPA, PASH and PAPASH syndromes, it could be explained from the physiopathogenic point of view, since all of these conditions exhibit overactivation of the innate immune response with an increase in IL-1β and TNF-α production, resulting in an excessive skin inflammation with tissue damage[25].

3.g. Emotional impact[26-29]

Psycho-emotional impact of HS is very high. Stigmatization, depression, irritability, embarrassment, isolation and anxiety on sexual contact result in low self-esteem and are the key indicators. Likewise, there is a significant relation between the different emotional states which seriously affect the quality of life of these patients and other comorbidities such as obesity, sedentary lifestyle, smoking and alcohol use. This is why the interdisciplinary approach in HS treatment is critical, since a great deal of investigation and psychological, and sometimes psychiatric, management is necessary, along with social assistance support for addiction recovery.

Approach is based on psychodermatology and psychoeducation so that the patient comes to know about the disease, providing tools, skills and techniques to improve his/her well-being. When disease

appears in adolescence, as it is a decisive period for the development of the individual identity, it is vital to act quickly to prevent their potential tendency to isolate themselves. This is considered the window of opportunity for psychological intervention. At the same time, it is important to work and educate, whenever possible, the people close to the patient, family members, friends, etc.

Psychological impact has been assessed using scales which apply to chronic diseases to monitor quality of life and symptoms, though they are not specific to HS. Those mostly used are the Dermatology Life Quality Index (DLQI) and the Hospital Anxiety and Depression Scale (HADS)[30,31].

4. DIAGNOSIS

It is based on clinical and ultrasound findings. There is no specific test for the diagnosis nor specific laboratory markers.

4.a. Clinical presentation

It is a chronic, recurrent, disabling disease that develops in flares. Prodromic symptoms (Table 1), which affect 80% of patients, may appear 12 to 24 hours before clinical manifestations[32].

Non-specific symptoms Fatigue (32%) Malaise (23%) Headache (11%) Nausea (2%)
Localized symptoms Erythema (75%) Paresthesia (63%) Pruritus (20%)

TABLE 1: Prodromes

Later on, non-inflammatory (without erythema and low sensitivity) and inflammatory (erythema and pain) nodules appear, which may resolve spontaneously after 7 to 15 days or progress to abscesses, fistulas or scarring (Figure 2).

Most frequent locations (Figure 3) are the following;

- Women: genital and inguinal regions (93%), axillary area (67%), intergluteal fold (33%), gluteus (23%), inframammary area and areola (22%).
- Males: axillary area (79%), genital (77%), intergluteal fold (51%), gluteus (40%) and inframammary region (5%).

There are less frequent locations, including, but not limited to, the nape of the neck, retroauricular region, abdominal waist, external ear duct, eyelids and navel[33]

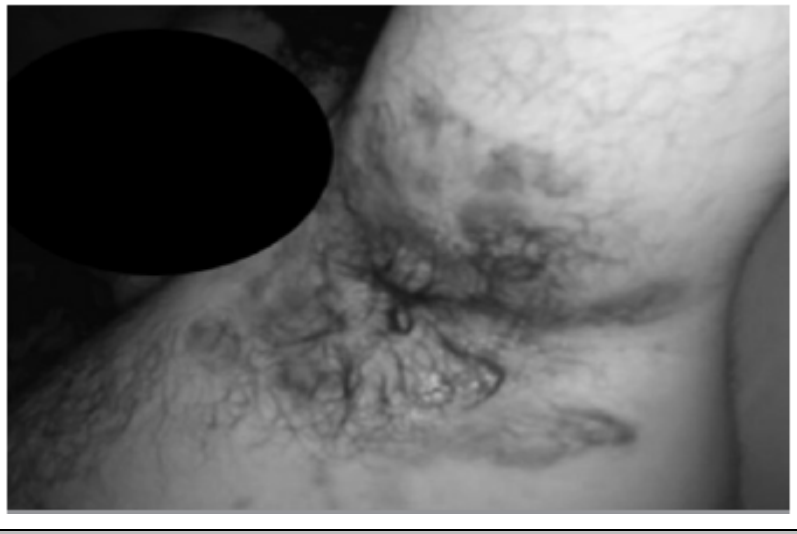

FIGURE 2: Clinical lesions

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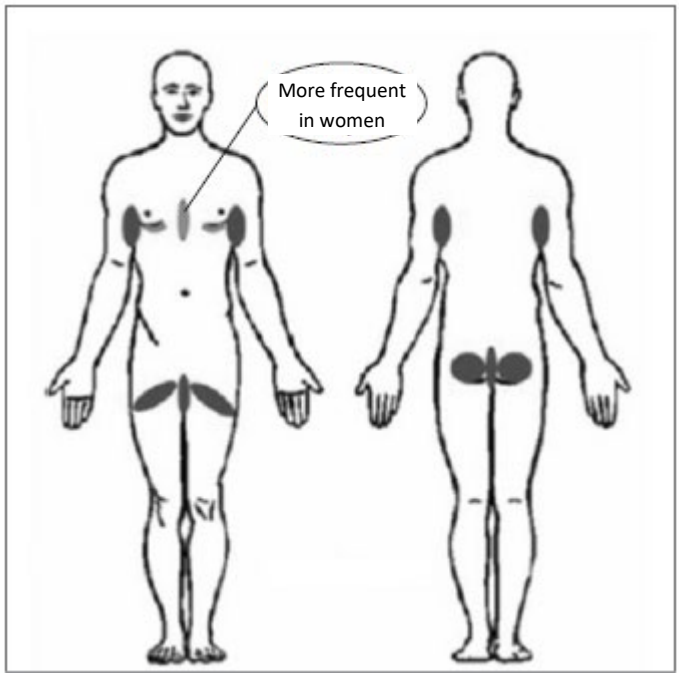

FIGURE 3: General anatomical sites

Clinical Diagnosis

- Typical lesions
- Localization
- Recurrence
- Other: family history, absence of fever and no adenopathies.
- Laboratory: C-reactive protein (CRP), as indirect inflammatory marker. It is a significant independent marker for Hurley III.

4.b. Ultrasound diagnosis[34]

The high-resolution ultrasound and the Doppler exam have played a prominent role in the latest years. Now there are 15-22 Mhz high-frequency linear probes, with a new technology which uses matrix transducers (Active Matrix Array Technology) and a higher Doppler sensitivity. It is a non-invasive method which uses no ionizing radiation nor contrast material, thus it is widely accepted by the general population.

Skin ultrasound allows to identify lesions not detected in the physical examination, and to duly assess its anatomical extent. In HS, ultrasound is preferred, since the 80% of lesions occur in the deeper layers and not in the surface of the skin. It allows to evaluate the exact location, the extent and echogenicity of lesions, the degree of vascularization on the Doppler exam and complications. In addition, it is useful to assess therapeutic response.

Ultrasound findings

- **Widening of hair follicles**: viewed as small longitudinal hypoechoic areas.
- **Thickening and abnormal echogenicity of the dermis:** it correlates with the presence of edema (hypoechoic) or fibrosis (hyperechoic).
- **Dermal pseudocystic nodules:** clinically, these correspond to inflammatory nodules. They are round- or oval-shaped images, discretely hypoechoic or anechoic, with posterior acoustic enhancement.
- **Fluid collections:** they are abscesses, hypoechoic or anechoic of different shapes and sizes, which can be located in the dermis or hypodermis. Hair can be found inside fluid collections as linear echoic images.
- **Fistulas:** true hypoechoic tracts which may or may not commuinicate collections with each other, with surface or depth. Martorell proposes to classify fistulas into four types comparatively based on the classification of fistulas in the intestinal inflammatory disease (Table 2 and Figure 4)[15].
- **Absence of adenopathies:** regional nodes are not increased in size.
- **Color Doppler:** it allows to evaluate different degrees of vascularization, mainly in nodules and collections, reflecting the inflammatory activity of the disease.

Group A: *Inflammed fistula, no draining and no scarring (simple dermal fistula)*
Group B: *Draining inflammed fistula with no scarring (simple dermoepidermal fistula)*
Group C: *Inflammed fistula with scarring (complex dermoepidermal fistula)*
Group D: *Deep inflammed fistula (inflammed hypodermal fistula)*

TABLE 2: Fistulas

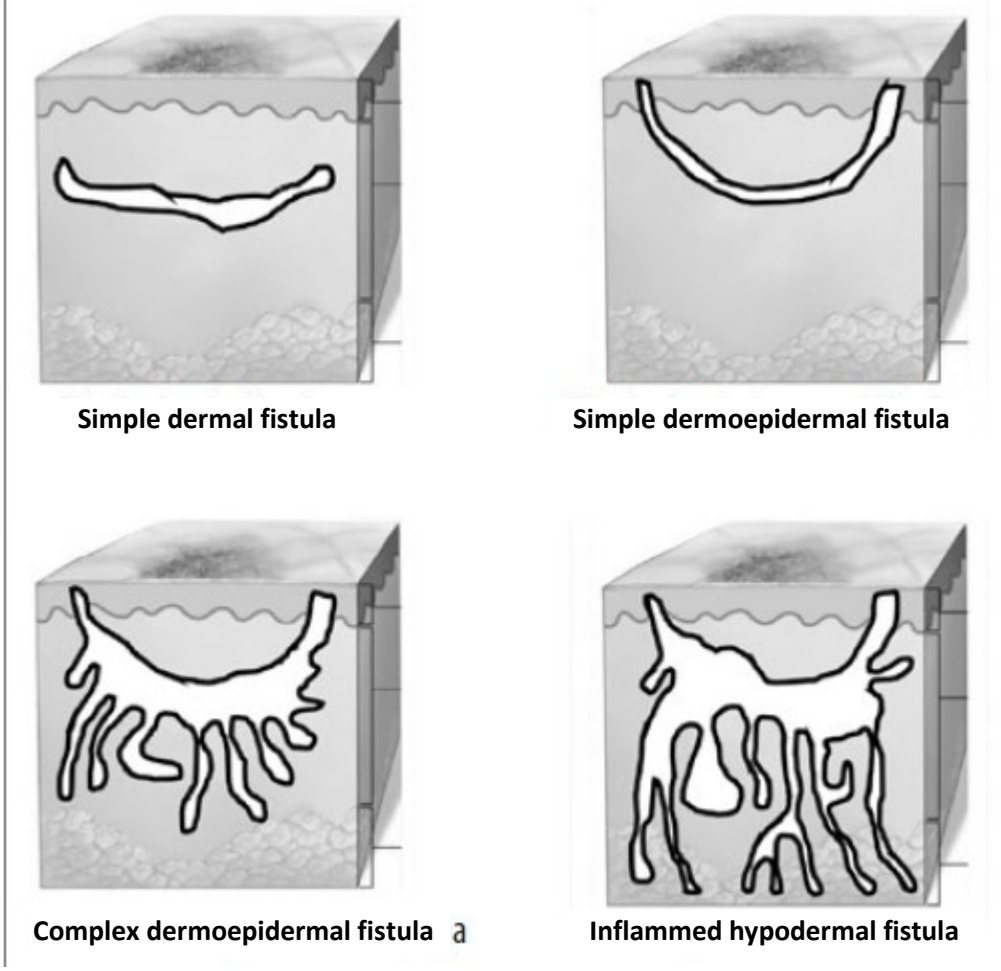

FIGURE 4: Classification of fistulas

***Ultrasound staging of hidradenitis suppurativa (SOS-HS)*:**

Wortsman et al. classified these ultrasound abnormalities using a sonographic scoring system called SOS-HS (Sonographic Scoring of Hidradenitis Suppurativa) for the staging of the disease into three stages[35] (Table 3).

I	Single fluid collection and dermal changes* affecting a single body segment (unilateral or bilateral) without fistulous tracts
II	Two to four fluid collections or a single fistulous tract with dermal changes* affecting up to two body segments (unilateral or bilateral)
III	Five or more fluid collections or two or more fistulous tracts with dermal changes* affecting three or more body segments (unilateral or bilateral)

TABLE 3: Ultrasound staging.

* Pseudocystic hypoechoic or anechoic nodules, widening of hair follicles, alterations in dermal thickness or echogenicity**.**

The isolated physical exam underestimates the severity of the disease in a significant percentage of HS patients. Therefore, ultrasound evaluation is essential for a true assessment of the patient, allowing the resulting staging to be essential for the establishment of an adequate treatment and follow-up.

Ultrasound examination protocol

Due to the multiple sites or areas affected by the disease, it is necessary that ultrasound examination evaluates all possible regions. In view of the high frequency of subclinical iinvolvement, it is suggested to initiate evaluation in the axillary and groin regions, then, the areas with clinically evident lesions and, finally, the areas with symptoms such as pain or pruritus, which tend to hide underlying lesions.

Ultrasound report should include:

- Anatomic location of the area involved and if unilateral or bilateral, e.g. right/left axilla, right/left groin.
- Location of lesions on the skin, if dermal, hypodermal or both.
- Number of nodules, collections and fistulas.
- Size of lesions measured in all three planes and, if possible, approximate volume in milliliters.
- Inclusion of hair inside the nodules or collections.
- Activity on the Doppler examination, if mild, moderate or severe.

Ultrasound monitoring of therapeutic response

A satisfactory therapeutic response is the reduction in the inflammatory activity. This phenomenon, many times clinically unnoticeable, translates into a decrease or absence of ultrasound activity in the Doppler examination. Repair of tissue damaged by inflammation will begin to be observed as hyperechoic areas covered by collections or fistulas.

4.c. Differential diagnoses

- **Staphylococcal infection**: it is a diagnosis with which HS is often mistaken, mainly in the presence of acute lesions. Staphylococcal lesions may be more extended, and present with adenopathies and fever. It may present with follicular pustules or furuncles. Treatment is based on antibiotic therapy[36].
- **Skin abscesses**: they are an accumulation of pus located in the skin; they may appear in any skin surface. Signs and symptoms are pain and fluctuant or firm edema. They require draining and therapy with antibiotics.
- **Anthrax or carbuncle**: it is an infectious condition with deep discharge, slow healing and scars. It is similar to HS due to the morphology of the skin lesions. However, ulcers caused by carbuncle are often painless. Treatment requires therapy with antibiotics[37].
- **Skin Crohn's disease**: clinically similar because of the presence of nodules and ulcerations. It may be suspected because of a history of intestinal involvement and relevant digestive symptoms. Biopsy can help, as well as faecal calprotectin measurement. Crohn's disease is a chronic granulomatous ulcerative inflammation of the intestine described in 1932 as "regional ileitis" Nowadays it is recognized it has a systemic involvement, thus it may also affect the cutaneous-mucous tissue[38].

- **Lymphogranuloma venereum**: it is a chronic, sexually-transmitted infection, which affects the lymphatic system, caused by *Chlamydia trachomatis*. It is characterized by the presence of an acute ulcer which progresses with tenderness and edema of the groin lymph nodes. It develops destroying internal and external tissues, with presence of pus and blood. Formation of fistulas, abscesses and stenosis is frequent. The destructive nature of lymphogranuloma also increases the risk of superinfection by other pathogens. Treatment requires antibiotic therapy[39].
- **Actinomycetoma**: it is a chronic granulomatous infection caused by filamentous bacteria, the most frequent being *Nocardia brasilensis* and *Nocardia asteroides*. It is an occupational condition usually appearing in middle-aged people of tropical countries who walk barefoot, especially in Mexico and Brazil. Inoculation is often traumatic after direct contact with thorns or contaminated plants, which can occasionally go unnoticed. The most frequent location is the lower limbs (60-75%), followed by the trunk, back and upper limbs. Mycetomas present clinically as nodules or plaques with multiple fistulas draining a serum-purulent material. Growth of lesions is slow and progressive, and may affect subcutaneous tissue, fascia and bones. Retractile scars are often observed[40].
- **Cutaneous tuberculosis (TB):** skin infection caused by *Mycobacerium tuberculosis*[22]. All cases require antibiotics according to the schedule for TB. Because of the epidemiological incidence in the country, various types of skin tuberculosis are described, depending on the clinical characteristics resembling HS: lupus vulgaris, tuberculosis verrucosa cutis, scrofuloderma, tuberculous chancre, tuberculosis *orificialis*, tuberculous gumma and cutaneous miliary tuberculosis[41].
  1. ***Cutaneous tuberculosis, ulcerative or orificialis type***: it is an endogenous re-infection. It is often periorificial, perianal and vulvar and it is associated with patients with extended lung TB. Skin lesions ulcerate from the beginning and show a progressive eccentric growth and poor healing. They tend to be painful, soft, punched-out, with raised and ill-defined margins. In the ulcer base there may be a pseudomembranous exudate. Course depends on seriousness of underlying cutaneous tuberculosis[41,42].
  2. ***Tuberculosis verrucosa cutis***: it is an infrequent clinical form, just like the primary cutaneous complex, of high resistance and of re-infection, in which the bacillus enters the skin by the exogenous route. It usually occurs in the back of the hand, though it may also occur in the plantar and juxtanal regions and in the intergluteal fold. It is clinically characterized by keratotic papules which, in their course, give way to verrucous plaques that progress on one end and scar over on another. It is chronic and, on certain occasions, it may regress spontaneously[41,43].
  3. ***Lupus vulgaris***: it is located in the middle of the spectrum and it is a form of moderate resistance. It is the most chronic and clamsy variant left in free evolution, and destructive. It can be seen in any stage of life and has a preference for the female sex. The most frequent locations are the head and the neck and, to a lesser extent, the limbs and trunk. It may affect mucous membranes from the beginning or by contiguity. It is almost always a single lesion, it is represented by tubercles or "lupomes" that leave scars on which new tubercles appear[41,42].
  4. ***Scrofuloderma***: It is the most frequent form of cutaneous TB in Argentina and of moderate resistance. It is part, together with gumma and pseudomycetoma, of the colliquative tuberculosis group, consisting of cutaneous TB forming cold abscesses with a tendency to spontaneous emptying. It is characterized by skin involvement from a mainly nodal

underlying tuberculous process. Other less frequent sites are: bone, joints, epididymis and lacrimal gland. The higher incidence occurs in children, adolescents and elderly. It is almost always located in the cervical region by regional nodal involvement and it is often unilateral. Lesions at the locations described soften and empty their content into the skin and in their course they leave a keloidal starred scar scattered with comedones[41,45].

4.d. Delay in the diagnosis

Historically, HS was considered a pyodermitis and treated by different specialties, without any one leading main management. This desentralization in medical care results in a major delay in reaching a diagnosis[46], plus the fact that patients feel embarrassed and seek medical care late, mainly women. The average delay in seeking medical care is estimated to be of 2.3 ± 5 years[47].

The reasons for the delay in diagnosis may be classified into two groups:

1. **Typical disease characteristics**: Lack of awareness of the physiopathology frequently leads to diagnostic errors, in addition to the lack of specific markers for disease confirmation, the use of dermatologic ultrasound not much spread in other specialties and the chronic natural history, characterized by flares.
2. **Characteristics relevant to the health system**: the patient may not have the possibility of consulting the same specialist or decides to attend an emergency room to solve that particular flare, which makes it difficult to detect lesion recurrence, one of the main diagnostic criteria for HS. It is estimated that patients visited an average number of 14.6 physicians of different specialties until a diagnosis was reached[11,48].
   It is important to increase awareness of healthcare workers in order to make an early and accurate diagnosis, aimed at initiating therapy as soon as possible and possibly help patients.

4.e. Complications[49]

Complications may be acute or chnonic, local or systemic:

a) **Acute**: since normal skin microflora has bacteria typical of cutaneous microbiome, superinfection is a frequent complication. This may be caused by contamination of the normal flora or as a secondary infection from a previously sterile process. Acute superinfection by *Staphylococcus aureus* or *Streptococcus pyogenes* is rare, as well as node involvement.
b) **Local chronic**: they may appear as a lymphatic obstruction, lymphedema and scrotal elephantiasis in patients with sustained and persistent genitourinary lesions. In long-term disease, urethral, bladder, rectal and peritoneal fistulas may occur. Squamous cell carcinoma usually appears in males on chronic lesions of 10 to 30 years evolution. Diagnosis usually comes late and prognosis is poor. Biopsies are recommended to be performed on old lesions, especially on those located on the buttocks. Other types of cancer may also be observed.
c) **Systemic chronic:** chronic discharge in extended disease, anemia, hyponatremia and amyloidosis.

5. CLINIMETRY

5.a. Classifications

Different scales are used (Hurley, Sartorius, among others) which allow to classify HS according to severity and to obtain objective measures of its clinical evolution and therapeutic response.

Hurley Method[50]

Proposed in 1989, it is the most widely used method to measure severity and it is based on three stages. It is not adequate to assess therapeutic response because it is static, non-quantitative and does not consider inflammatory activity. Its relevance is limited to the potential surgical indication. However, it is required by our healthcare system as a standard for therapeutic prescription. Stage I corresponds to mild HS, single or multiple abscesses with no scarring and no fistulas. Stages II and III correspond to the moderate and severe forms; stage II is characterized by the presence of one or more recurrent abscesses with formation of fistulas and scars, and stage III by similar lesions but they involve an entire region.

- **Modified Hurley Method**[51]
  It was modified in 2016 by the Dutch expert group headed by Prens & Van der Zee. In this new classification the evaluation of sinus tracts, areas involved, degree of inflammation and different phenotypes are taken into account to personalize therapy.
  Patients in the original Hurley I-II stages may be considered serious. Hurley III is re-defined as patients with 1% involvement of body surface and inflammatory interconnected sinus tracts.
  These changes help choose therapy between antiinflammatory agents and/or surgery, and to prescribe biologics to Hurley I patients who are considered serious (IC) or when surgery is not appropriate (Figure 5).

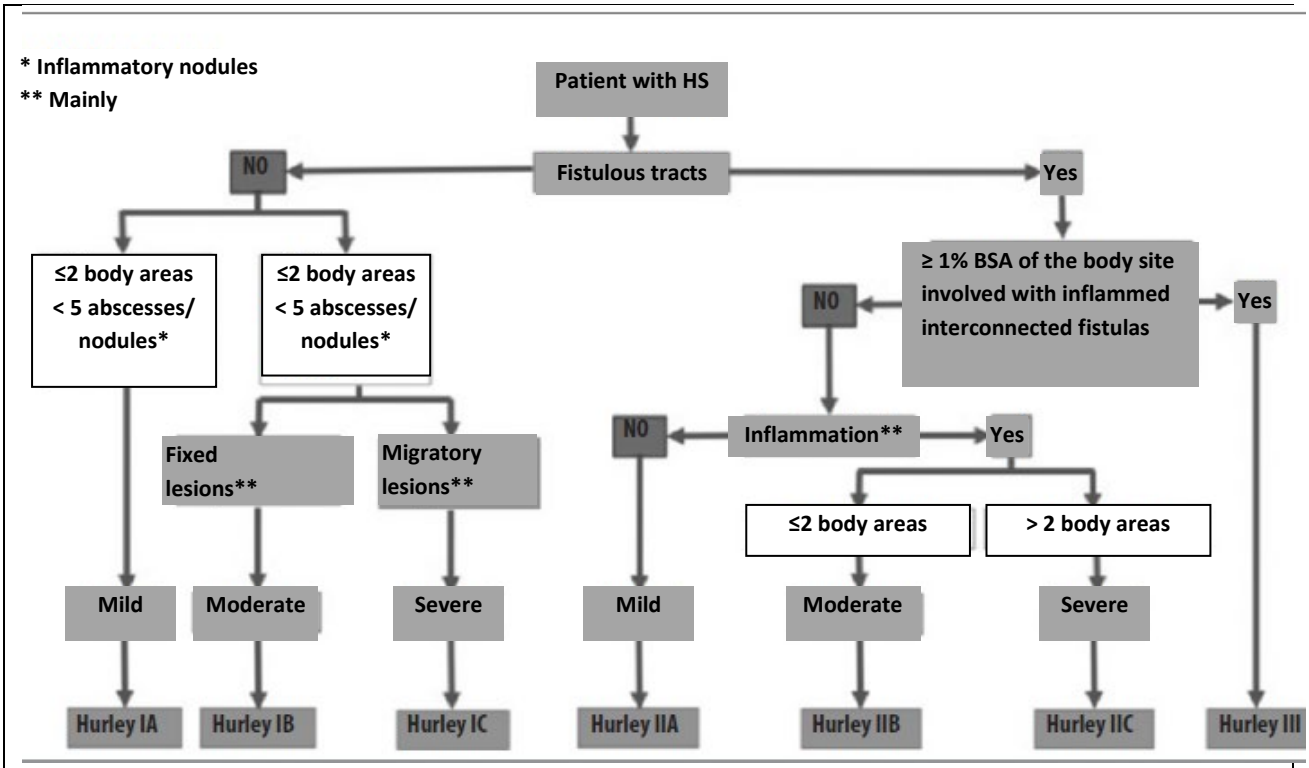

FIGURE 5: Modified Hurley Method
Adapted from English. BSA: body surface area

Sartorius Scale[52]

In 2003 Sartorius described a detailed and dynamic scoring system of the severity of HS, updated by Revuz in 2007 and again modified in 2009 by Sartorius, which is the one currently used (Table 4). This classification is based on the count of individual nodules and fistulas, facilitating the dynamic measurement of clinical severity. Disadvantages are reflected in severe cases when lesions converge, it does not consider inflammatory lesions and administration and interpretation are time-consuming for healthcare personnel.

Physician Global Assessment (PGA)[53]

PGA describes levels of severity considering the presence of inflammatory and non-inflammatory nodules, draining and non-draining abscesses, and fistulas. It was used to measure the inflammatory activity and therapeutic response until HiSCR. One of its disadvantages is the variability among observers (Table 5).

Anatomical region involved (three points per region)
Axilla
Groin
Genital
Gluteus
Inframammary
Other (nape, retroauricular, upper and lower limbs, umbilical, etc.)
Number and score per lesion
4 points per fistula
2 points per abscess or nodule
1 point per scar
1 point per other lesions
Greater distance between two relevant lesions
8 points: > 10 cm
4 points: 5.1-10 cm
2 points: < 5 cm
Are lesions separated by normal skin?
0 points: yes
6 points: no

TABLE 4: Sartorius Scale (modified)

0	Clear	0 abscesses, 0 draining fistulas, 0 nodules
1	Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules (IN) and presence of non-inflammatory nodules (NIN)
2	Mild	A. 0 abscesses, 0 draining fistulas and up to 5 (IN) B. Single abscess or draining fistula, no (IN)
3	Moderate	A. 0 abscesses, 0 draining fistulas and more than 5 (IN) B. Single abscess or draining fistula, and presence of (IN) C. 2-5 abscesses or draining fistulas, with or without (IN) up to 10
4	Severe	2-5 abscesses and draining fistulas with or without (IN) >10
5	Very severe	More than 5 abscesses or draining fustulas

TABLE 5: Physician Global Assessment (PGA)

Clinical response in HS (HiSCR – Hidradenitis Suppurativa Clinical Response)[54]

It captures the most acute phase of activity by counting inflammatory nodules and abscesses. It does not contradict the analysis of response as per PGA or modified Sartorius, but it represents a more accurate element of therapeutic response. HiSCR does not consider the size or seriousness of lesions, it does not allow staging of the patient and does not measure the level of pain or the patient's quality of life. It is based on objective measures and provides a result which is effective, convenient and easy to use in the clinical practice. It was used in clinical trials, such as in the PIONNER I-II. It is based on the course of disease and has a significant value when therapeutic response shows a 50% reduction in inflammatory nodules, with no onset of new nodules or new fistulas.

Hidradenitis Suppurativa Severity Score System (IHS4-International HS 4)[55]

This staging system corrects and improves the difficulties posed by the previous ones.

It allows to establish grades of severity bearing in mind the number of nodules, abscesses and draining fistulas assigning them a scoring system. It is validated by the European HS Foundation (EHSF) and it is easy to use. It evaluates the inflammatory response and the therapeutic efficacy. With this methodology it is expected to facilitate the standard clinical use, allowing the assessment of therapeutic response and save time (Table 6).

Score per lesion	Number of lesions	Result
Nodule 1 point	X	1X = A
Abscess 2 points	Y	2Y = B
Fistula 4 points	Z	4Z = C
Final score		**=A + B + C**

TABLE 6: IHS4 estimation

Staging according to the summation of points	
Mild	3 or less
Moderate	4-10
Severe	11 or more

5.b. Phenotypes

Initially, three phenotypes were known (subtypes of HS)[56]:

1. **Axillary mammary**: it affects 48% of patients, with hypertrophic scars.
2. **Follicular**: it affects 26% of patients, located in breasts and axillas, trunk, ears and lower limbs. Typical lesions are comedones, epidermal cysts, severe acne and pilonidal cyst.
3. **Gluteus**: it affects 26% of patients, with follicular papules.

In 2015, Van der Zee et al. added five additional types to these three phenotypes: frictional furuncle, scarring folliculitis, *conglobata*, syndromic and ectopic[57] and, in 2018, Romani described the cervical type[15]. However, currently patients are classified based on elementary lesions and their ability to progress, for which two general subtypes were described[58]:

1. **Follicular**: 70% of patients, with no later progression. Typical lesions are open and closed comedones, and the main active lesion is the superficial or deep nodule. Abscesses and fistulas are scarce and superficial and appear during adolescence. Pruritus is the most frequent symptom. In the presence of family history, the onset of a larger number of nodules is expected. Only 8% progresses to the inflammatory phenotype.
2. **Inflammatory**: 30% of patients, with ability to progress and more aggressive. Typical lesions are abscesses and fistulas, thus they have a small follicular component (nodules and comedones). Onset is generally in young adults. Pain and smell are the most frequent symptoms. In the presence of family history, a greater aggressiveness is expected. In this phenotype IHS4 is higher, as well as serum IgA concentrations.

6. THERAPEUTIC GUIDELINE

Currently, different HS therapeutic guidelines coexist in the world. The most frequently used are the European S1 guideline for the treatment of HS/acne inversa (2015)[1] and the Evidence-based approach to the treatment of HS/acne inversa, based on the European guidelines for HS (2016)[58]. According to the various degrees of severity, recommendations for the first-, second- and third-line treatment are made using the GRADE approach[59,60] (Table 7). Surgical recommendations will be developed later on.

The HS work group of the Argentine Society of Dermatology (SAD), based on prior evidence and experience of its members in HS therapy, proposes the following recommendations for patient treatment and follow-up (according to standards, evidence and expert recommendations):

First-Line		
Topical clindamycin	IIb	Possible B
Clindamycin/rifampin p.o.	III	C
Tetracycline p.o.	IIb	B
Adalimumab	Ib	A
Second-Line		
Zinc gluconate p-o.	III	C
Topical 15% resorcinol	III	C
Intralesional corticosteroids	IV	D
Systemic corticosteroids p.o.	IV	D
Infliximab IV (off-label)	Ib/IIa	B
Acitretin/etretinate p.o.	III	C
Third Line		
Colchicine p.o.	IV	D
Botulinum toxin s.c.	IV	D
Isotretinoin p.o.	IV	D
Dapsone/sulphone p.o.	IV	D
Cyclosporine A p.o.	IV	D
Acetate/finasteride p.o.	IV	D
* p.o.= oral route; s.c.=subcutaneous		

TABLE 7: Therapies (Evidence – Recommendation).

6.a. General non-pharmacological measures

The following measures are suggested as general indications in diagnosed HS:

- Use appropriate clothing: no study has published information about the use of specific clothes or a methodology for cleaning HS lesions. According to our experience, the use of loose clothes to prevent mechanical stress made of non-synthetic fibers is recommended.
- Identify and correct risk factors (tobacco, sedentary lifestyle, diet, alcohol and other) and comorbidities (overweight/obesity, metabolic syndrome, intestinal inflammatory diseases, arthropathies, etc.).
- Improve hygienic conditions and suggest hair removal (laser/IPL).
- Diet[61]: there are no studies of solid scientific evidence; however, there have been reports of a fair response to dairy-, sugar-, refined flour- and yeast-free diets. Zinc supplements, vitamin D and turmeric may be beneficial. Some patients benefit from recording their diets to find triggers of flares. Nutritional service assistance is suggested in case of implementing specific diets.

- Medical interdisciplinary evaluation according to comorbidities and therapy indication (in case of planning immunosuppression).
- Psychological or psychiatric support.
- Non-steroidal pain-killers, stressing the need to avoid self-medication.
- Coadjuvant therapy (resorcinol, zinc gluconate): there are no formal studies recommending this therapy. These agents are recommended as second-line treatments, though we prefer to classify them as coadjuvant therapies, given their low efficacy. **Topical 15% resorcinol**, twice daily, was proposed based on a series of 12 cases, with partial improvements, mainly in Hurley I-II stages after drainage of lesions. It usually causes contact dermatitis[62]. **Zinc gluconate, 90 mg/day orally** is proposed as a "restorer of innate immunity". Twenty-two patients in Hurley I-II stages with partial responses in 63% of the cases were studied. Iron absorption may be impaired[63].

6.b. First-line therapy

6.b.1. Antibiotics

The use of t**opical 1% clindamycin** was based on a 12-week study conducted by Clemmensen (1983) in 27 Hurley I-II patients. The most significant effect was observed on superficial lesions and the effect on deep lesions such as nodules and abscesses was very poor or absent[64]. However, patients using topical clindamycin were more likely to develop *Staphylococcus aureus* antibiotic resistance (63%)[65].

In a controlled trial conducted by Jemec (1998) which compared the efficacy of 0.1% clindamycin versus tetracycline 500 mg orally, no difference was found in clinical improvement of nodules, abscesses or pain[66]. Oral tetracycline does not cause antimicrobial resistance when used as per medical instructions[15]. Therefore, systemic antibiotic is preferred, and topical therapy is to be avoided in all stages of disease.

Systemic **clindamycin and rifampin** combined therapy was based on a study conducted by Van der Zee (2009)[67], which took into account Hurley stages and different doses and durations of treatments. It was concluded that the most effective schedule is to use clindamycin 300 mg and rifampin 300 mg every 12 hours orally for 10 weeks and then evaluate therapeutic response. There are two studies conducted by Gener (2009)[68] and Mendonca (2006)[69] that recommend combined therapy. Since Argentina is an endemic TB country, we do not recommend the use of rifampin to prevent resistance. The use of clindamycin did not generate significant antimicrobial resistance, based on studies presented at the 2018 EHSF congress[15].

6.b.2. Biologics

6.b.2.1. Getting ready for immunosuppression or immunotherapy

It will be evaluated according to each drug in particular, taking into account side effects and contraindications. As to biologic therapies, we propose to bear in mind the following considerations before using an anti-TNF.

- General laboratory tests: complete blood count, liver and kidney function tests, lipid profile, blood glucose and other (as per each patient's history and risk factors).
- Serological tests for TB (PPD or quantiFERON), HIV, syphilis, Chagas disease, toxoplasmosis, hepatitis B, C and A.

- Chest X-ray
- Dental monitoring.
- Screening for tumor and neurological conditions according to age and prevalence.
- Complete immunization schedule. It should be remembered that, if possible, vaccines should be administered 4 weeks before initiating therapy. In addition, in the case of yellow fever vaccine, it should be administered 4 weeks before initiating biologic therapy and, if already on biologic therapy, it should be discontinued for 3 months before vaccine administration. In newborns from mothers on treatment with biologics, live or attenuated vaccines are contraindicated during the first 5 months of life (immunodepression through placental transfer of the drug). Together with the pediatrician, breastfeeding duration should be evaluated taking into account the possible presence of the drug in breast milk.
  The following schedule is suggested:

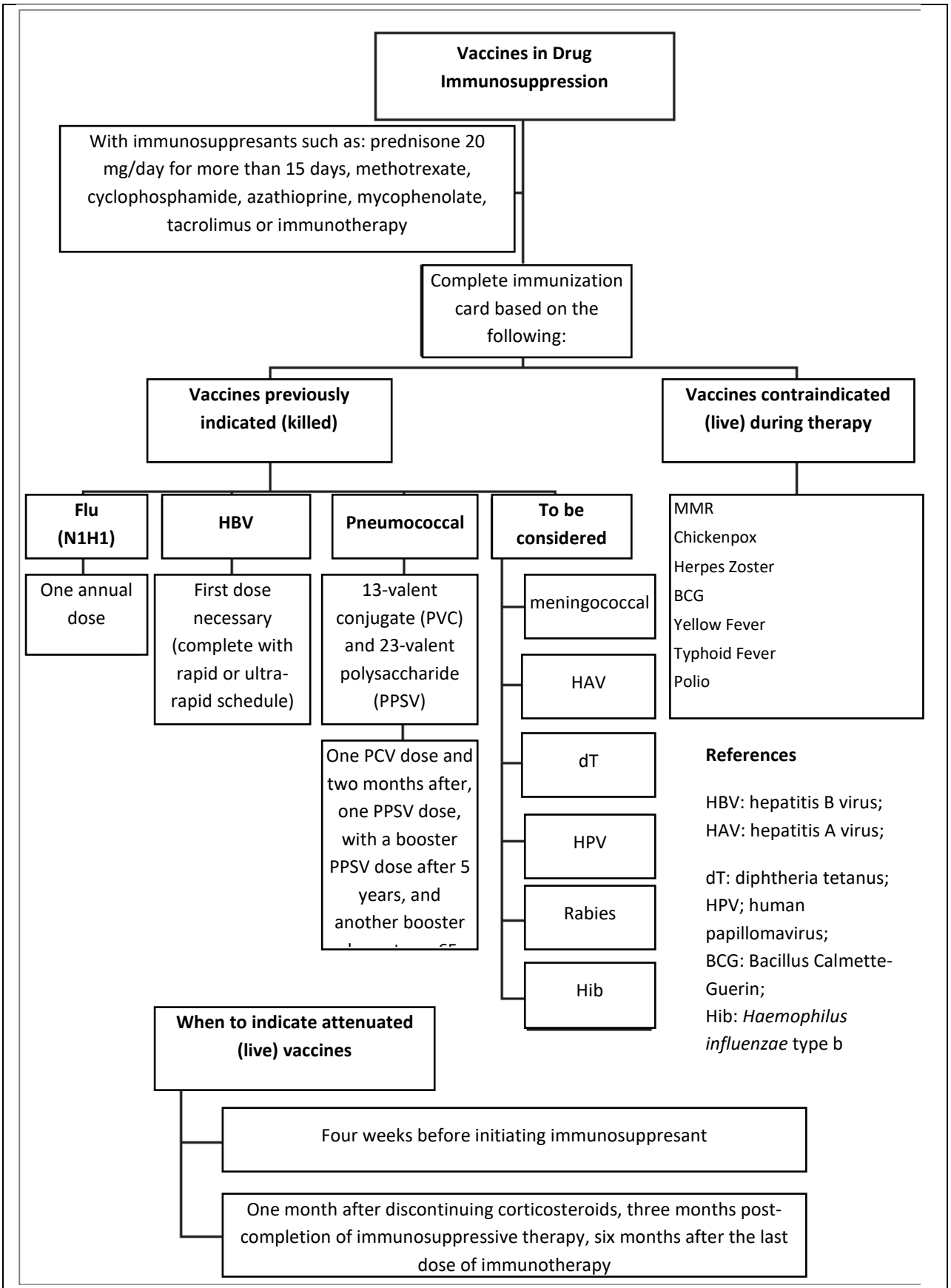

FIGURE 6: Immunization schedule for dermatology patients (Servicio de Dermatología Clínica Universitaria Reina Fabiola)

6.b.2.2. Anti-TNF Drugs

We refer to the two therapies addressed in the treatment guidelines (Table 8), though there are several published papers with other anti-TNF and anti-interleukine therapies.

Considerations prior to the institution of an anti-TNF therapy:

- It predisposes to an increase in upper respiratory tract infections, skin and soft tissues; opportunistic infections (histoplasmosis, mucocutaneous candidiasis); parasitic and viral infections (HZV/HSV). It is of utmost importance to remember reactivation, infection or re-infection by *Mycobacterium tuberculosis*, which is more related to the use of anti-TNFs because of the immune inhibition for granuloma formation. Mucocutaneous candidiasis is mainly associated with the use of biologics with anti-IL-17 activity, without this being exclusive to a specific type of drug. That's why we stress the need to prepare for immunotherapy as described above.
- Hepatitis B reactivation.
- The onset or recurrence of demyelinating diseases with anti-TNFs are to be taken into account, though other drugs are not excluded as potential triggers.
- In Class I and II heart failure it is recommended to perform an echocardiogram prior to treatment and in Class III-IV heart failure (NYHA classification) anti-TNF therapy is contraindicated. In these cases, consultation is recommended with a cardiologist before initiating treatment with a biologic agent.
- Hypersensitivity reaction to the active ingredient or to any of the inactive ingredients.
- Autoimmune processes may be exacerbated (psoriasis, vasculitis, erythema nodosum, Sjögren's syndrome, systemic lupus erythematosus and autoimmune hepatitis). They are called paradoxical reactions, interpreted as *de novo* induction cases, or worsening of these conditions. It was suggested that impaired balance between TNF and interferon-α would be involved in its etiopathogenesis.
- In general, surgeries may be performed without discontinuing biological therapy, except for major surgeries (dirty) that so requiere.
- Pregnancy and breastfeeding: adalimumab and infliximab have no indication in this respect, though there are isolated studies of its use in these cases.

Adalimumab

It is the first and only biological approved so far by the FDA and the EMA for the treatment of moderate to severe HS. As from 2015, Argentina has ANMAT approval. A Phase II[70] study and two Phase III (PIONEER I-II)[71] studies have been conducted, in addition to an extension (OLE) study. HiSCR response rates of 50.6% have been observed in the consolidated analysis of Phase III studies after 12 weeks of therapy, with Hurley II (53.6%) and Hurley III (47.3%) improvements. The extension study concluded that HiSCR rates were almost 60% after 72 weeks, with tolerability and adverse events within expectations.

In the adult population, a treatment schedule was defined, with initial subcutaneous doses of 160 mg (week 0), 80 mg (week 2) and 40 mg after week 4, once a week. ***We currently have an 80 mg pre-filled syringe, which is indicated for maintenance, administered every 14 days***. This improves adherence and reduces healthcare costs in our country.

Its use is approved in adolescents >12 years of age or in those weighing at least 30 kg. Pediatric dosage was determined using a pharmacokinetic model, with initial doses of 80 mg (week 0), followed by 40 mg every 15 days, starting at week 1. In patients with inadequate response, 40 mg/ week may be administered[72].

Infliximab

Grants et al. (2010) conducted the first formal evaluation (Phase II) of infliximab in moderate to severe HS versus placebo. A dose of 5 mg/kg was used at weeks 0, 2, 4, 6 and every 8 weeks, with a 50% decrease in the HS severity index (HSSI), significant changes in DLQI and in the visual analogue scale and decrease in erythrocyte sedimentation rate and C-reactive protein. Placebo group treated with infliximab after week 8 showed a similar response. No unexpected adverse events were observed[73]. Two prospective studies conducted by Paradela et al.[74] and Lesage et al[75] (2012) have been reported, as well as five retrospective studies conducted by Sullivan et al. (2003)[76], Fardet et al. (2007)[77], Fernández-Voz- mediano and Armario-Hita et al. (2007)[78], Delage et al. (2011)[79] and Moriarty et al. (2014)[80]. Dissimilar results and inconsistent dosing schedule were seen in all cases. It is currently used off-label, since it has not been approved by the FDA.

Biologic therapies	
Adalimumab (on-label)	Day 0: 160 mg s.c. Day 14: 80 mg s.c. Day 28: maintenance 40 mg s.c. (every 7 days) 80 mg s.c. (every 14 days)
Infliximab (off-label)	Initial dose: 5 mg/kg at weeks 0, 2, 4 and 6 Maintenance dose: 5 mg/kg every 8 weeks

TABLE 8: Dosing Schedule

6.c. Second- and third-line therapy

6.c.1. Corticosteroids

Intralesional triamcinolone (5-10 mg/mL) has been suggested because of its fast anti-inflammatory effect in acute cases to treat painful nodules. It is used in combination with other systemic therapies in refractory and flare cases. Adverse events include atrophy, pigment changes and telangiectasias. Systemic effects are rare and it is not recommended in cases of superinfection[81].

Systemic corticosteroids[82] have anti-inflammatory, immunosuppressive, anti-proliferative and vasoconstrictive effects, and countless adverse effects which lead to close evaluation of its use in HS patients. The drug of choice is meprednisone at doses of 0.5-0.7 mg/kg/day. There is limited data on its benefits and they are associated with reduction in acute inflammation and management of flares rather than with sustained partial remissions. The following should be evaluated before use: blood pressure, weight, blood count, kidney and liver function, blood glucose, lipids and the presence of osteoporosis.

Contraindications include active infections and diseases which can exacerbate with the use of corticosteroids. It interacts with erythromycin, clarithromycin and rifampin. Use should be evaluated in pregnant women because of the risk of neonatal adrenal suppression.

6.c.2. Retinoids

Acitretin is used because of its influence on the cornification cycle, normalizing cell differentiation and thinning the corneal layer by reducing keratinocyte proliferation. It inhibits chemotaxis of polymorphonuclear cells and proinflammatory mediators. Doses vary between 25 and 50 mg/day, for a duration of 6-12 months, with variable response rates (40%-60%). It is worthwhile commenting that this drug is teratogenic, and it has deleterious effects on the liver and lipid profile. The presence of cheilitis and xeroderma is frequent, and rare that of alopecia, pruritus, xerophthalmia, paronychia, central nervous system disorders, peripheral neuropathy, intracranial hypertension, flushing, epistaxis, rhinitis, stomatitis, gingivitis, nausea, vomiting, dysgeusia, rectal bleeding, night blindness, myalgias and pancreatitis.

Contraindications:

a) Absolute: sexually active women of child-bearing potential not using a highly effective contraception, pregnancy (up to 3 years after discontinuing medication), breastfeeding, liver or kidney disorders, alcohol abuse, blood donors and pancreatitis.
b) Relative: dyslipidemias and use of contact lenses. Drug interactions: tetracyclines, methotrexate and vitamin A[83,84].

Isotretinoin is a drug heavily studied in HS, with many papers presented but poor response (16%) and relapse rates (13%). Indicated dose is 0.5-1 mg/kg/day. Adverse effects and contraindications are the same as those established for the treatment of acne[85,86].

6.c.3. Antibiotics

Dapsone[87,88] is a sulfone with antibacterial and antiinflammatory properties used at doses of 25-200 mg/day. Clinical improvement is observed in 38% of cases and relapses in up to 8%. The dose and the adequate duration of therapy was not established. This therapy may be used in advanced refractory stages. Before initiating treatment, blood count, reticulocyte count, liver and kidney function and glucose-6-phosphate dehydrogenase (G6PD) values should be available.

Contraindications include G6PD deficiency, allergy to sulphas, anemia and acute porphyrias. It interacts with trimethoprim and rifampin. It is not teratogenic, but crosses the placental barrier and may cause neonatal hemolysis and metahemoglobinemia (third trimester of pregnancy). Use during breastfeeding is not recommended.

6.c.4. Other

It was suggested that ***colchicine***[89] be used at doses of 0.5 mg every 12 hours due to its potential suppression of caspase-1 activation and inhibition of IL-1β release. A prospective study was conducted in 8 patients with poor efficacy, thus it would not be indicated in this entity.

Adverse effects include gastrointestinal disorders, alopecia, neuropathy and hepatic and renal toxicity.

Botulinum toxin is defined as an investigational therapy in mild cases; we do not recommend its use[90,91].

Cyclosporine A[92,93] is a calcineurin inhibitor with immunosuppressive activity. It has beneficial effects in limited cases. It has various adverse effects: blood hypertension, kidney toxicity, liver

toxicity, non-melanoma skin cancer, lymphoproliferative changes, increased risk of infections, dyslipidemias, gingival hyperplasia, hypertrichosis, hypomagnesemia and hyperuricemia.

As to contraindications, these are classified into:

a) **Absolute**: history of cancer, renal failure, uncontrolled hypertension, liver viral disease or other, treatments with concomitant phototherapy, live or attenuated vaccines.
b) **Relative**: pregnancy, breastfeeding, alcohol abuse, nephrotoxic and hepatotoxic drugs, uncontrolled infections, HIV, HCV and immunodeficiencies.

Drug interactions include: barbiturates, carbamazepine, oxcarbazepine, phenytoin, IV sulfamidine, orlistat, *Hypericum perforatum* (St John's wort), ticlopidine, sulfinpyrazone, terbinafine, bosentan, rifampin, nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, folic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazodone, macrolide antibiotics, azole antifungals (ketoconazole, fluconazole, itraconazole and voriconazole), verapamil, amiodarone, danazol and diltiazem.

Antiandrogens such as ***cyproterone acetate*** (100 mg/day) and estrogens improve HS, while progestogens induce or worsen it. They are usually indicated in women with menstrual disorders, signs of hyperandrogenism and high levels of DHEA or androstenedione. Favorable responses are described in several cases, but there are no evidence-based studies[29,31]. Adverse effects include headache, chest pain, nausea, dysmenorrhea, increased weight, sinusitis, flu symptoms and abdominal pain[94].

6.d. Laser therapy

Carbon dioxide laser as surgical treatment and Nd:YAG as hair removal therapy are proposed. Both are included in the group of first-line therapies with evidence Ib category and recommendation A level.

- **Carbon dioxide**[95,97]. Three studies from 2002 to 2015 with 12, 61 and 58 patients, respectively, were considered for indication, and an acceptable efficacy and recurrence was demonstrated. In one of the studies, 91% of patients would recommend CO_2 laser surgery.
- **Nd:YAG**[98,99]. Only two studies in a total of 44 patients showing an acceptable percent reduction in severity have been considered, though recurrencies were not taken into account.

6.e. Surgical therapy[15]

There are several techniques according to skin lesions. **Incision and drainage** with a scalpel blade is recommended when lesions are painful nodules or abscesses. This allows to relieve the pressure, drain the content and relieve pain. **Deroofing** using scissors, electrosurgery and/or CO_2 laser is recommended, with prior use of local anesthetics, and in spite of being combined with antiinflammatory therapy in the presence of recurrent Hurley I-II lesions. This decreases recurrences and complications. **Wide surgery** performed by surgeons specialized in Hurley II-III stages with type C-D fistulas is recommended. It reduces recurrences and inflammation and prevents the onset of malignant processes. In surgeries < 50 cm^2 the secondary intention closure or the primary closure

with anatomical reconstruction is considered. In wider surgeries (< 50 cm^2) skin graft is recommended. In both cases, negative pressure therapy or hyperbaric chamber may be used.

Mandatory Indications for the surgical procedure[15]:

- Sinus tracts
- C-D type fistulas (no response to systemic therapy, including adalimumab).
- Rope-like and contracture scars.
- Mutilating HS
- Malignant tumors (squamous-cell carcinoma, adenocarcinoma)

7. THERAPEUTIC ALGORITHM

Modified window of opportunity

This concept was addressed at the International Congress of Dermatology (Milan, 2019), under the authorship of doctors A. Lavieri, C. Greco and M. Bittar, defined as the anticipation of biologic therapy prescription (Hurley IA with SOS-HS II, IB and IC ultrasound) with no escalation with other prior therapies. This therapeutic shortcut is justified based on the auto-inflammatory physiopathogenesis of HS and the specific inhibition of its clinical progress, so that the patient's quality of life improves dramatically. The possibility of discontinuing biologic therapy without the onset of lesions at least for a long time, and thus reduce healthcare costs (Figure 6) still remains to be considered in later studies.

- **HURLEY IA**

  If HS involves up to two anatomical sites with less than five nodules/abscesses and absence of sinus tracts, a Doppler ultrasound of the skin is recommended, not only of the areas involved, but also extending it to areas not clinically involved at the time of evaluation. This allows to stage the patient (clinical-echographic correlation) and to establish the right therapy within the ***modified window of opportunity***, to prevent disabling progress altering quality of life.

  In Hurley IA stage, the presence of nodules (non-inflammatory or inflammatory) is observed. In the case of non-inflammatory nodules, surgical excision and prophylactic systemic antibiotic therapy are recommended. If inflammatory nodules are found, systemic antibiotic therapy with NSAIDs is indicated or not, pending resolution or to facilitate subsequent resection.

  An evaluation every 12 weeks with HiSCR is suggested: in responders, maintain therapy; in non-responders, institute biologic therapy. If the patient has off-treatment flares with a frequency of every 6 months or more, re-start the antibiotic schedule and evaluate potential surgery.

  In the case of Hurley IA with echo-Doppler stage SOS-HS II or III, indicate biologic therapy and surgical treatment according to the response of collections or fistulas.

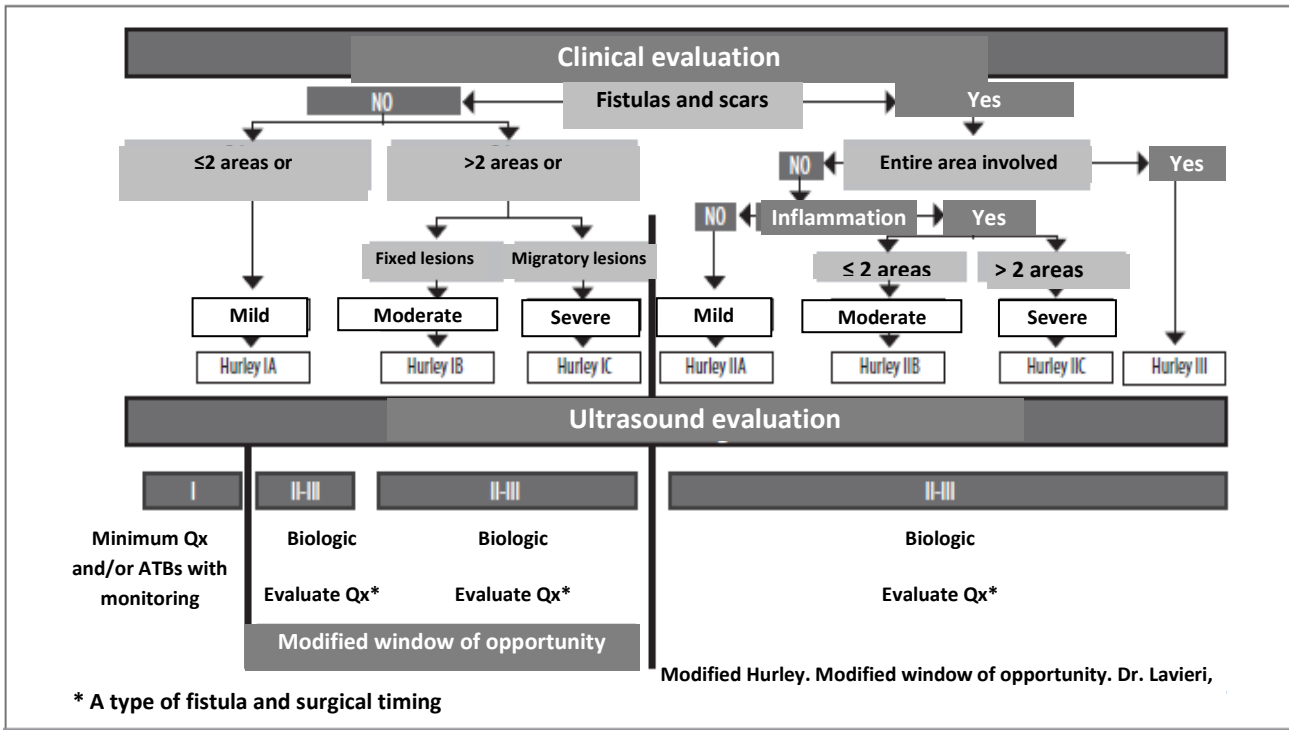

FIGURE 7: Therapeutic algorithm

- **HURLEY IB/C**
  Indicate starting biologic therapy. Wait for resolution of nodules and, if not achieved, indicate surgical therapy without discontinuing biologic therapy. Echo-Doppler evaluation does not modify the initial treatment, but it will be useful to evaluate the presence of sub-clinical collections or fistulas and determine the actual clinimetric score (to be performed at the time of diagnosis) and to evaluate therapeutic response (3 months after initiating treatment).

- **HURLEY IIA/IIB/IIC/III**
  In these cases there is a systemic inflammatory impact (comorbidities and CRP). It is suggested to indicate biologic therapy in all cases to reduce the number of flares and their intensity. The patient's quality of life will always be highly influenced by the disease, the true window of opportunity having been missed. Surgical therapy is not only used for resection of inflammatory sites but also to improve anesthetic scars, quality of life (mainly mobility) and tumor prophylaxis. Ultrasound is useful to evaluate evolutionary response to therapy and surgical timing.

- **Flares in any stage**
  Indicate systemic antibiotics without discontinuing background therapy (*see Antibiotics*) and/or systemic or intralesional corticosteroids. In case of failure of therapeutic response, institute second- and third-line treatments, as per the 2016 European guideline[58] (*see Table 6*).

8. CONCLUSION

The adaptation of the algorithm presented, where Hurley modification, its association with the ultrasound classification and the choice of therapy are linked in a new interpretation of the window of opportunity facilitates the implementation of a timely and adequate prescription and achieves the key objective: to improve the quality of life of patients.

First consensus: October 6, 2019
Version 1.2019
Planned review: December 2020.

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