



**EFFICACY AND SAFETY OF NEGATIVE PRESSURE WOUND THERAPY IN
TREATING HIDRADENITIS SUPPURATIVA AND REDUCING ITS RELAPSES: A
RANDOMIZED CONTROLLED CLINICAL TRIAL**

Final Degree Project

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1. ABBREVIATIONS

AB: Antibiotic

AEMPS: Asociación Española del Medicamento y Productos Sanitarios

ASA: American Society of Anesthesiologists

BMI: Body Mass Index

BnTX: Botulinum toxin

CEIC: Comitè Ètic d'Investigació Clínica

CI: Contraindication

CNs: Coagulase Negative Staphylococci

CRA: Clinical Research Associate

DLQI: Dermatology Life Quality Index

ECM: ExtraCellular Matrix

HS: Hidradenitis Suppurativa

HSSI: Hidradenitis Suppurativa Severity Index

IL: Interleukin

NPWT: Negative Pressure Wound Therapy

NSAID: NonSteroidal Anti-Inflammatory Drugs

PGA: Physician Global Assessment

QoL: Quality of Life

SAPHO: Synovitis, Acne, Palmar pustulosis, Hiperostosis, Osteítis

SECPRE: Sociedad Española de Cirugía Plástica, Reparadora y Estética

SPSS: Statistical Package for the Social Sciences

STSG: Split Thickness Skin Graft

TLR2: Toll like receptor 2

TNP: Topical Negative Pressure

VAC: Vacuum Assisted Closure

VAS: Visual Analog Scale

χ^2 : Chi Square

2. ABSTRACT

Background Hidradenitis Suppurativa is a chronic, debilitating disease with high psychosocial impact. It is neglected by physicians despite affecting 1% of the population because of its difficult treatment and low healing rate. The physiopathology is not currently clear. Nodules, sinus-tracts and/or scarring predominate in the folds of the body, mostly in axilla, sub-mammary groin and buttocks. Medical treatment can be effective in first stages of the disease, but surgical procedures are needed for treating severe cases. Wide local excision offers the best chance for cure, although all surgical techniques have a high relapse rate.

Purpose The main purpose of this study is to show a decrease in the number of recurrences in HS patients operated using a technique that combines radical wide excision with the use of NPWT followed by skin grafting or flapping in a second surgical intervention.

Design Randomized, controlled unicentric clinical trial design will be carried out in a tertiary referral hospital in Girona within a Plastic Surgery department.

Participants Patients suffering from Hidradenitis Suppurativa stage III of Hurley, or stage II where conservative treatment has failed, been seen at Hospital Universitari Dr. Josep Trueta, Hospital Sta Caterina, Fundació Hospital d'Olot and Hospital de Palamós.

Key words hidradenitis suppurativa, vacuum-assisted closure, split thickness skin grafts, wide excision

3. INTRODUCTION

3.1 HIDRADENITIS SUPPURATIVA

Definition

Hidradenitis suppurativa (HS), also called ‘acne inversa’ or ‘Verneuil¹’s disease’ is a “chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions (Dessau definition, 1st International Conference on Hidradenitis suppurativa/Acne inversa, March 30–April 1, 2006, Dessau, Germany)”(1)

Epidemiology

The exact prevalence of HS in general population can only be estimated. There is an important variability and uncertainties concerning the actual frequency.(1) It depends on how and where data is gathered, suggesting the presence of significant bias and coding issues(2). It is estimated that in Europe there is a prevalence of 1% of the population.(1) Normally this illness appears on people on their twenties or thirties and it's three times more common in female versus males(3), affecting 4% of young adult women(1). This difference lowers in women after the menopause (3). **Figure 1** outlines the epidemiology.

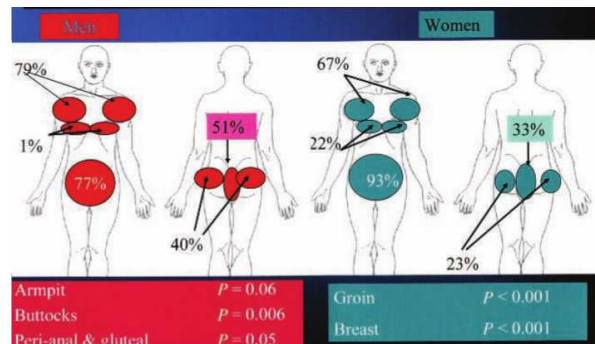


Figure 1. Locations prevalence in both sexes; the statistical differences between men and women are shown(21)

Pathogenesis

The etiology of the disease is unknown, but current theories can be grouped in five blocks:

1. **Genetic** (5% of the cases (1)): families with an autosomal dominant mode of inheritance have been identified. It seems to be related with loss-of-function mutations of gamma-secretase genes involved in Notch cell signalling pathways(4). There is a possible relation between TNF gene mutation and increase in disease severity that gets better with TNF- α agents(1).

¹ Aristide Auguste Stanislas Verneuil was a French surgeon who in the mid-nineteenth century associated this disease with an alteration of the apocrine glands and named it HS.(20)

2. **Environmental factors:** number of years smoking, tight clothes, deodorants and waxing products are predisposing factors to suffering from HS. In particular obesity and smoking are also correlated with lower rates of disease remission(5).
 - **Obesity:** considering overweight at BMI 25-30, obesity at BMI \geq 30 and severe obesity at BMI \geq 35. Association with HS:
 - More than 75% obese patients
 - 77% of males being overweight and 26% obese
 - 69% of females being overweight and 33% obese
 - 51.6% obese, with 21.5% severely obese
 - **Tabaco:** widely renowned severe risk factor although there is no data about the temporal relationship between smoking and the first manifestations of HS(1)
 - **Mechanical stress:** It is suspected to act as a “trigger for the outburst of new lesions”. This statement is based on the opinion and testimony of patients saying that wearing tight clothes induces outburst of lesions. Leg stump lesions can be consequence of mechanical friction as well. Pathological studies have evidenced the fragility of the dermo-epidermal junction that could justify the facts explained above.(1)

3. **Endocrine** cause is suspected because disease onset is more common in puberty and its incidence is reduced after the menopause and during pregnancy in women(3). Obesity, metabolic syndrome and hypertension are also risk factors to get HS(5).

4. **Microbiological factors:** HS does not follow a standard pattern of an infectious disease: there is no unique bacterial agent but a polymorphic flora. Carrying out bacterial samplings of suppurations, the samples were sterile. It is common to find several batteries of the normal skin flora in the HS lesions. Coagulase Negative Staphylococci (CNS) in sweat glands can be detected either as contaminants of the normal skin flora or as the result of a secondary infection of an initial sterile process(1). Bacterium found in sample lesions are described in **Table 1**. It is unclear whether this infection represents colonisation of sinuses or is pathogenic(3).

Area affected	Bacterium
Axillae + Genitals	<i>Staphylococcus hominis</i>
	<i>Staphylococcus epidermidis</i>
	<i>Staphylococcus haemolyticus</i>
Axillae + Perineum + Groin	<i>Micrococcus species</i>
	<i>Micrococcus luteus</i>
	<i>Micrococcus varians</i>
Axillae + Groin	<i>Acinetobacter</i>

Table 1. Areas affected by different bacterium(1)

5. **Drugs:** oral contraceptives and lithium(6)

Inflammation process

Inflammatory reaction mechanisms leading to HS are known just in some measure. It is suspected to be an occlusion of the upper parts of the hair follicle leading to a perifollicular lympho-histiocytic inflammation. An important trigger factor explaining the chronic inflammation is the overexpression of toll like receptor 2 (TLR2) that induces an increase of macrophages and dendritic cells infiltration. Macrophages infiltrating papillary and reticular dermis of HS skin express pro-inflammatory cytokines IL-12 and IL-23. These interleukins are responsible for mediation of autoimmune tissue destruction. In concrete, IL-23 is involved in the induction of T helper cell subset producing IL-17 (also called Th17). In chronic HS lesions Th17 infiltrates the dermis. It is known that IL-1 β , CYCL9 (MIG), IL-10, IL-11 and BLC are overexpressed cytokines and IL-20 and IL-22 are down regulated.

Pathological Anatomy

Although the histological study is not necessary to determine the diagnosis, some alterations in the tissues have been described. It's considered that a change of the follicular terminal epithelium causes an occlusion of itself in areas where abound apocrine glands:

- **Early inflammation pattern:** neutrophilic abscess formation and influx of mainly macrophages, monocytes and dendritic cells predominate (1) creating spongiform inflammatory changes under the infundibulum. Openings of hair follicle can be blocked by quarantine plug resulting in a rupture of the follicle and subsequent inflammation that dilate the duct(6).
- **Established lesions:** show follicular plugging, follicular cysts, reduced volume of sebaceous glands, psoriasiform hyperplasia, neutrophilic abscesses, sinus tracts lined by a stratified epithelium(1).
- **Chronic severe pattern:** infiltration expands creating winding tracts (some of them fistulous), subcutaneous abscesses with increased frequency of B cells, plasma cells in 'pseudo' follicles, abscesses and sinuses surrounded by a chronic inflammatory infiltrate containing histiocytes and giant cells, granulation tissue and plasma cells. All this can lead to an extensive fibrosis in the dermis at the end. (1)(6)

The absence of IL-17 in infundibular-like keratinized epithelium grants fragility of the draining sinus epithelium and can conduce it to the rupture. Fragility can be explained by the presence of PAS positive material in the borer and the centre of the lesions of sebo-follicular junctions.

Clinical presentation

European S1 guideline for the treatment of hidradenitis suppurativa (1) defines HS clinical presentation as "Recurrent inflammation occurring more than 2x/6 months or 3x/6 months in the inverse regions of the body, presenting nodules, sinus-tracts and/or scarring". The most typical areas affected are those ones with more density of apocrine gland-bearing such as the

axilla, groin and perianal (5). Patients describe pain as “hot, burning, pressing, stretching, cutting, sharp, taut, splitting, gnawing, sore, throbbing or aching.” It can be a consequence of deep seated inflammatory nodules. The level of pain has been evaluated by the Visual Analog Scale (VAS). (1)

First symptoms can be nonspecific (pruritus, erythema and local hyperhidrosis) followed by pain, induration with subcutaneous nodules, and finally abscesses that can drain malodorous material in a chronic way. Every time it recurs, the initial cavity gets bigger. This is due to a subcutaneous fibrotic cavity net gets formed and it gets interconnected by the fistulous tracts.(6) It can be accompanied by extra cutaneous features (arthritis, interstitial keratitis) and associate constitutional symptoms (i.e., fever and malaise).(5)

Diagnosis

HS diagnosis is eminent clinic.(6) HS patients can be seen by diverse medical specialties: surgeons, emergency physicians, plastic surgeons, infectious disease specialists, general practitioners, and dermatologists, but they are often neglected by most. This is because there are no standard criteria to diagnose this disease and no curative treatment has been defined yet. This results in dissatisfaction of the patient and unmet of his needs. The diagnosis is often delayed by 5 to 14 years highlighting an unfulfilled need for medical assistance. (2)

Despite of this, European S1 guideline for the treatment of hidradenitis suppurativa (1) has defined some diagnostic criteria:

- **Primary positive diagnostic criteria**
 - o *History*: Recurrent painful or suppurating lesions for more than 2x/6 months
 - o *Signs*: Involvement of axilla, genitofemoral area, perineum, gluteal area and infra-mammary area in women. Presence of nodules (inflamed or non-inflamed). Sinus tracts (inflamed or non-inflamed), abscesses, scarring (atrophic, mesh-like, red, hypertrophic or linear).

- **Secondary positive diagnostic criteria**
 - o *History*: Family history of HS.
 - o *Microbiology*: Negative swab or the presence of normal skin microbiota

Diagnosis differential (1)

- Staphylococcal infection (lesions are spread in a random fashion and more pustular)
- Cutaneous Crohn’s disease ([see Comorbidities Associated in p.10](#)).
- Simple abscesses (usually single lesions)
- Neoplasms, primary or secondary (systemic and histological signs of tumour)
- Lymphogranuloma venereum
- Rare:
 - o Cutaneous actinomycosis (presents with sinus tract disease)
 - o Scrofuloderma type of cutaneous tuberculosis

Classification and severity

There are three common ways to classify HS: **Hurley** (more clinically applicable; **Table 2**), **Sartorius** system (used especially in the area of research; **Figure 2**)(5) and **Physician global assessment (PGA)** (used to measure clinical improvement in clinical trials of medical treatments; **Table 3**) (1)

HURLEY	Characteristics	Prevalence
Stage I	Abscess formation, single or multiple, without sinus tracts and scarring	68%
Stage II	Recurrent abscesses with tract formation and scarring, single or multiple, widely separated lesions	28%
Stage III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area	4%
Limitations: not quantitative, consisting of only three stages and based on static disease characteristics such as scarring and fistulas. It is not suitable for monitoring the efficacy of interventions in clinical trials.		

Table 2. Hurley classification to describe HS severity(1)

Sartorius Score is computed by counting individual nodules and fistulas(1) of involved regions, nodules and sinus tracts. It is based on the salient clinical features of the disease, and allows a more dynamic description of disease severity(7). It is used to determinate the severity assessment. Its main restrictions are:

- In severe cases separate lesions can become confluent(1)
- It is designed to document the treatment outcomes following surgery. It may not adequately reflect changes following medical therapy (7).

Anatomical region involved (three points per region involved)

- Axilla
- Groin
- Gluteal
- Intramammary left/right
- Other

Number and scores of lesions

- 2 points for abscesses/nodules
- 4 points for fistulae
- 1 point for scars
- 1 point for others

The longest distance between two relevant lesions

- 2 points if <5 cm
- 4 points if <10 cm
- 8 points if >10 cm

Are all lesions separated by normal skin?

- 0 points if yes
- 6 points if no

Figure 2. Sartorius score(7)

Physician global assessment (PGA)	
Clear	No inflammatory or noninflammatory nodules
Minimal	Only noninflammatory nodules
Mild	Less than five inflammatory nodules or one abscess or draining fistula and no inflammatory nodules
Moderate	<5 inflammatory nodules or 1 abscess or Draining fistula + 1 or more inflammatory nodules or 2–5 abscesses or Draining fistulas < 10 inflammatory nodules
Severe	2–5 abscesses or draining fistulas + >9 inflammatory nodules
Very severe	>5 abscesses or Draining fistulas

Table 3. PGA scale to determinate the severity of the illness. Frequently used in clinical trials of medical therapies(1)

There are other scores less used such as Kerdel or Hidradenitis Suppurativa Severity Index (HSSI) (specific severity score for the illness)(1).

Comorbidities associated

There are numerous comorbidities associated to HS:

1. **Metabolic syndrome**, statistically and clinically significant(2)
2. **Obesity**(1)(5)
3. **Crohn's disease**. In initial stages both illnesses can be clinically indistinguishable. The association between both illness is so hard that some authors consider that HS is a cutaneous manifestation of Crohn's disease(6).
4. It is a physical and mental debilitating illness (6) that can conduce to **depression** and **anxiety disorders** also statistically and clinically significant(2).
5. Autoimmune diseases marked by systemic inflammation, such as **Crohn's disease** (2). Some studies have associated the perianal HS with the coexistence of Crohn's disease(6). In fact, in some cases it is hard to difference them or to confirm the coexistence of both(5).
6. Congenital déficits of **alfa1-antitripsina**(6)
7. Stigma related to the smell and the stains in clothes, pain, diminished quality of life, declines in disability and diminish in **work productivity** (2)
8. **Acne conglobata**: severe acne localized in pectoral, back and buttocks region consisting mainly of comedones and small purulent nodules (6).
9. **Dissecting cellulitis of the scalp** (*perifolliculitis capitans*): similar to the above but affects the scalp and can cause alopecia (6).
10. **Pilonidal sinus** (6)

The association of acne conglobata, dissecting cellulitis of the sclap and hidrosadenitis suppurativa is also called **Follicular occlusion triad**; while the combination of the three previous dermatologic illnesses with pilonidal sinus is called **follicular occlusion tetrad**.

Complications

The aim complications found in the bibliographic review are collected in **Table 4**.

Complications	
Acute	Super-infection: <i>S. aureus</i> +/- <i>S. pyogenes</i> (rare)
	Enlarged lymph nodes (unusual)
Chronic	Lymphatic obstruction → Lymphoedema
	Scrotal elephantiasis
	Fistulization of HS lesions to the rectum, vagina, urethra, peritoneum and/or bladder
Cancer	Aggressive squamous cell carcinoma (10-30 years of evolution lesions). Diagnosis tardy → prognosis very poor <i>Biopsy should be performed in every long-lasting lesion of the gluteal area</i>
	Chronic suppuration in severe widespread disease
Systemic complications	Analytic changes: anemia, hypoproteinemia, hypertriglyceridaemia, hypo-HDL-cholesterolaemia, hyperglycaemia(1)
	Amyloidosis
Reumatological disorders	Axial reactive arthritis
	Peripheral arthritis (dactylitis)
	Enthesopathies
	SAPHO
Psychosocial impact	Spondylarthropaties
	The skin is the largest and most visible part of the body. That is the reason why an alteration on it has a big psychosocial impact. This impression can be objectified with the quality of life (QoL) – Dermatology Life Quality Index (DLQI). HS has a large effect on patient's QoL, DLQI is altered in 60% of examined patients. <ul style="list-style-type: none"> - Depression (21%) - Stigmatization. Promotes isolation due to fear of stigmatization - Sexual health (female>male). Embarrassment and pain

Table 4. HS complications(1)

Treatment

Therapeutic management of HS will be adapted according to the severity and localization of the illness. The main objective will be the improvement of the QoL. More clinical trials are needed to demonstrate therapies' efficacy in the long-term. (6)

As we have explained in the diagnosis, generally patients with HS have been treated by a different number of specialties, but owned by none(2). In this section we are going to explain adjuvant therapy, medical treatment and different surgical procedures studied at this time. General indications for choosing which treatment may be the best option are represented in the following **Figure 3**.

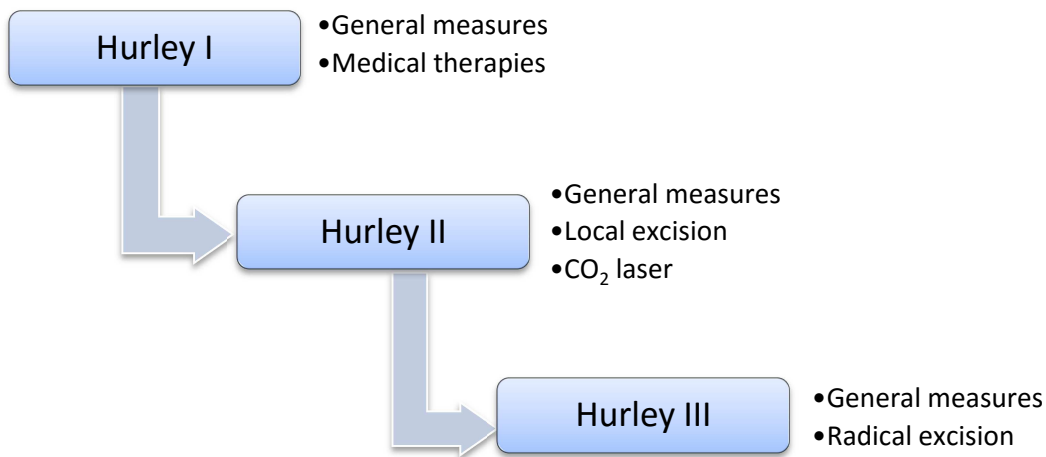


Figure 3. Therapeutic algorithm for HS according to the severity of the disease(6)

Adjuvant therapy

Even though there are no trials or studies supporting this recommendation, some procedures collected in **Table 5** are recommended apart from the medical and surgical treatment:

General measures	Stop cigarette smoking
	Reduce overweight
	[Use of chlorhexidine/other aseptic washes and bacterial swabs of lesions] There is no evidence on it, because superficial bacterial flora at the skin surface is not likely to play significant role in the physiopathology
Bandages	Customized due to anatomical variation; absorbent and nonirritant (keep the surface dry and absorb smell) Specific HS-bandages are not still available
Psychosocial support	No specific studies are available yet

Table 5. General therapies to combine medical or surgical therapies(1)

Medical therapy

Numerous drugs have been tested for healing HS, but their efficacy is not very high. All the therapies studies by the moment are collected in **Table 6**. Topic and systemic antibiotics such as Clyndamicin are the most common drugs administrated for HS stage I and II.

MEDICAL THERAPY		Drug	Mechanism of action	Indication	Dosage	Response with respect to placebo	Most recurrent complications
Topic	Nonantibiotic	Topical resorcinol	Keratolytic, antipruritic and antiseptic	Localized Hurley I or II	15% resorcinol cream 2x/d	Improves lesional draining	Irritant contact dermatitis
		Adapalene/ Azelaic acid	<i>No formal studies have been conducted</i>				
	Antibiotic (AB)	Clindamycin	Binds to 50s ribosomal subunit of bacteria → disrupt transpeptidation → disrupt protein synthesis	Localized Hurley I or mild stage II	Apply cream during 3 months	Significant 4.5-fold better improvement	Stinging and skin irritation Selection of resistant bacterial strains.
Systemic AB	Tetracycline	Bind to the 30S ribosomal subunit reversibly → prevents the binding of the amino acyl tRNA and thus translation	Widely spread Hurley I or mild II disease	500 mg/12h for 4 months	30% reduction of severity	Microbial resistance Concomitant use of oral contraceptives Teratogenicity	
	Clindamycin-Rifampicin	Clind: already explained Rif: Inhibits DNA-dependent RNA polymerase activity in bacteria, by interacting with bacterial RNA polymerase	Any stage active inflammatory HS	300 mg /12h for 10 weeks	50% reduction in Sartorius score	Gastrointestinal adverse effects	
Anti-inflammatory	Intralesional corticosteroids (triamcinolone acetonide)	Rapid reduction in inflammation	Recalcitrant nodules and sinus tracts	5–10 mg/ml	Seen in 48–72h	CI: clinical suspicion of bacterial infection Atrophy, pigmentary change and telangiectasia	
	Systemic corticosteroids	Anti-inflammatory immunosuppressive, antiproliferative and vasoconstrictive effects.	Short term: reduction in inflammation associated with acute flares Long term: rebound flare on withdrawal	0.5–0.7 mg/kg oral	Limited data	CI: untreated systemic infection Rebound disease flare on therapy withdrawal	

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Anti-inflammatory	Dapsone	Antibacterial (inhibition of dihydrofolic acid synthesis) Anti-inflammatory (inhibition of chemoattractant-induced signal transduction, suppressing neutrophil recruitment and local production of toxic respiratory and secretory products)	Mild to moderate disease (Hurley I or II)	25–200 mg a day	38% significant clinical improvement	CI: severe G6PD deficiency, sulphonamide allergy, severe anaemia and acute porphyria. Interactions: trimethoprim, rifampicin Haemolysis, haemolytic anaemia, methaemoglobinaemia, hypersensitivity syndrome, agranulocytosis and eipheral naeuropathy
	Cyclosporin A	Calcineurin inhibitor with potent immunosuppressive activity	Failure of 3 first line of therapy	2–6 mg/kg for 6 weeks–7 months	Moderate response after 6 weeks	CI: infection, uncontrolled hypertension, malignancy and high cumulative doses of psoralens and UVA Nephrotoxicity, hypertension and risk of malignancy
	Hormones	Antiandrogens and estrogens improve Progestogen worsen	Females with menstrual abnormalities, hyperandrogensim or ↑dehydroepiandrosterone, androstenedione and/or sexual hormone-binding protein	100 mg/d	No evidence-based data	Mild headache, breast pain, nausea, dysmenorrhoea, neurosity, gain weight, sinusitis, influenza-like symptoms, abdominal pain.
Biologics	Adalimumab	Human monoclonal antibody (IgG1, TNF-α)	Hurley I or II	160mg/d	>50% improvement was detected	CI: Heart failure NYHA class III – IV, severe infection, pregnancy and lactation Respiratory and urinary tract infections
	Infliximab	Chimeric monoclonal antibody against TNF-α	Hurley I or II	5 mg/kg/d	>50% improvement was detected	CI: Heart failure NYHA class III-IV, Hypersensitivity to mouse proteins, severe infection, pregnancy and lactation Minor infections, keratoacanthoma and hepatitis

Retinoids	Isotretinoin	Bind to retinol-binding proteins or retinoic acid nuclear receptors to accelerate cell-cycle progression, cellular differentiation, cell survival and apoptosis	Prevent an affected pilosebaceous unit from being occluded by ductal hypercornification Not recommended.	0.5–1.2 mg/kg for 4 -12months	Disappointing.	Retinoid dermatitis, headache, arthralgia, tiredness, mood changes, skin fragility, nose bleeds, myalgia
	Acitretin / Etretinate	Helps to normalize cell differentiation + thin cornified layer by reducing the keratinocytes' proliferation	Hurley I or mild II	0.25–0.88 mg/kg/d	Good results	Retinoid dermatitis, hair loss, ↓night vision, alterations in lipids profile, headache, ↓concentration, joint pain, buzzing in ears and depression/fatigue
Analgesics	Nonsteroidal anti-inflammatory drugs (NSAID)	Analgesic, antipyretic and anti-inflammatory Block cyclooxygenase enzymes → ↓prostaglandins → ↓pain and inflammation	Amelioration of acute pain	600mg/8h	No clinical evidence exists	Renal failure, liver failure, ulcers and prolonged bleeding time, cardiovascular events
	Opiates	Bind to opioid receptors → ↓pain intensity	When all other painkillers have failed	Usual dosage of codeine and hydrocodone	No evidence-based data	CI: liver + renal impairment and severe pulmonary failure Opioid dependence
Zinc gluconate		Alteration of innate immunity in lesional skin	Maintenance in Hurley I and II	90 mg/day	Promising results	Gastrointestinal
Intra-muscular gamma-globulin		Immunomodulation → ↓inflammatory reaction	Use currently not recommended	12.38 mg/kg/d	50–70% improvement	CI: IgA deficiency, thrombocytopaenia or other coagulation disorders Pain and erythema at the injection site Shock, anaphylaxis, deep vein thrombosis and ↓intravascular coagulation, ↓renal function
Colchicine		inhibits microtubule polymerization inhibiting several cytokine signalling pathways	Poor efficacy. Use currently not recommended	0.5 mg/12h for 4 months	No evidence-based data	CI: severe liver or kidney dysfunction, haematological disorders, gastrointestinal disturbance
Experimental	Botulinum toxin(BnTX)	Unknown	Hurley stage I or II HS	40 – 250 units	No evidence-based data	CI: Infection in the area to be injected or allergy to BnTX

Table 6. Medical Therapy for HS gathered from the "European Guideline for HS" (1)

Surgical therapy

The kind of surgery and success getting free margins will depend on the body region and severity of the disease. Some authors advocate performing colostomy when intervening in perianal region to prevent further infections(6).

1. Conventional surgery

Excision or curettage of individual regions (Electrosurgical procedure)

- *Procedure:* Repeated electrocauterization and curettage of the draining sinuses may be curative
- *Indication:* Grade I and II
- *Drawback:* High recurrence rate

Radical excision of the lesions and surrounding hair-bearing skin

- *Procedure:* Complete excision of the apocrine gland bearing area delineated by the hairy surface(s) of the affected region (s) + 1-2cm of margin(6). The method of reconstruction has no influence on recurrence and should be chosen with respect to the size and location of the excised area
- *Indication:* Treatment of choice for HS.

No reconstruction (second intention healing)

- *Procedure:* Excision of the affected skin and closure by secondary healing – without reconstruction
- *Drawback:* lengthiness due to prolonged healing

Primary closure

- *Indication:* Less extensive defects and certain anatomical situations allow primary closure

Reconstruction with immediate or delayed skin grafting

- Split thickness skin graft (STSG) coverage of the exposed area either immediately or in a delayed fashion, 10–14 days later, is an extensively accepted method.
- *Drawback:* 33% recurrence

Reconstruction with skin grafting and NPWT

- Wide surgical excision and skin grafting complemented with negative pressure wound healing therapy (VAC therapy) results in better outcomes. **This will be the technique evaluated in this clinical trial.**

Reconstruction with flap plasty

- *Procedure:* Myocutaneous flaps for reconstruction
- *Indication:* Recurrent disease
- Defect coverage with fasciocutaneous and musculocutaneous flaps can be carried out with an acceptable recurrence rate therefore being recommended as a reasonable alternative
 - o use of a stool management system or colostomy for perineal/perianal lesions
 - o use of a thoracodorsal artery perforator flap may increase upper limb movement significantly

It is very difficult to compare surgical treatment modalities for HS because of the complex nature of the disease, the numerous complicated surgical interventions widely used for treatment and the variable results reported in the literature. More comparative studies are needed to move disease status from being a disease of incapacitated patients and frustrated physicians.

2. Deroofing

Effective and fast technique indicated to Hurley 1 or 2 that consists of introducing a blunt probe in sinus openings. Then surgically remove the roof of the lesion using the probe as a guide. Thanks to the use of electro-surgical loop, good hemostasis is achieved, allowing in this way good visualization of the operative area. Created defects will heal by secondary intention.

3. Carbon dioxide laser therapy

- *Procedure:* "Focal radical vaporization of all nodules, abscesses and fistulas, leaving healthy tissues in between the pathological lesions. The lesions are vaporized from 'inside and out' until surrounding healthy tissues are reached, superficially and deep. In this way the technique can be tissue sparing and at the same time radical."
- *Other indications:* excise smaller or larger skin areas in bloc with or without laser coagulation of remnants (marsupialization) in the deep tissues, with less bleeding and better visualization than in standard excisions

4. Nd: YAG laser therapy

- *Procedure:* It consists in a neodymium-doped yttrium aluminum garnet laser, designed for hair removal
- *Response:* The effects appear to maintain 2 months after the fourth laser treatment.
- More work is needed before Nd:YAG laser can be established as a standard treatment for HS.

5. Experimental therapies

IPL therapy

- *Procedure:* By reducing the number of hairs in anatomical regions with a predilection for HS to occur, it is assumed that HS-recurrences would be less likely in those regions

Photodynamic therapy

- Short-contact 5-aminolevulinic acid-PDT therapy using blue light for activation and a 3-month follow-up period. All patients had a total or almost total clinical improvement.

Recurrences

They are more common in inguinoperineal (37%) and submammary (50%) areas than in perianal (0%) and axillary (3%) in 3-72 months after the intervention (6).

In a Ritz study (8) patients were observed after a follow up of 72 months. According to the procedure performed there were different recurrence rates:

- 100% after incision and drainage, with half of recurrences three months after surgery
- 42.8% after local excision, with an average of 11 months
- **27% after radical excision, with an average of 20 months**

3.2 NEGATIVE PRESSURE WOUND THERAPY

NPWT is a non-pharmacological, physical method for wound healing care that consists on the application of local subatmospheric pressure across a wound (Figure 4)(9).

In this trial we have decided to work with VAC® system brand for being the one with more published clinical evidence than any other form of TNP (10) and for being the one used in Hospital Josep Trueta of Girona where the study will be done. Moreover, it is the most common and vastly used in the market and previous studies have been made with it (so, our outcome will be easier to compare with them).

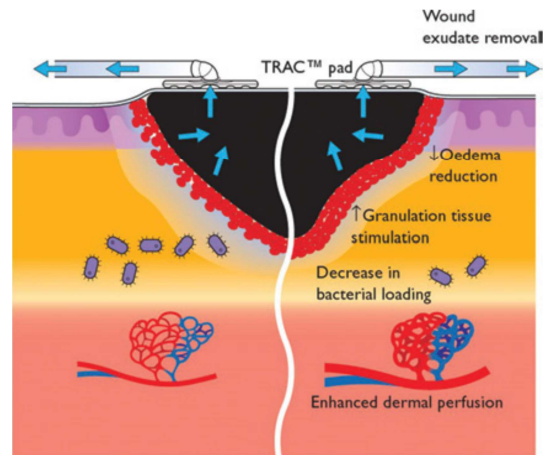


Figure 4. Postulated mechanisms of action of topical negative pressure(9)

There are several mechanisms of action explaining its functionality(9) graphically represented in Figure 5:

- An increase in wound perfusion
 - A reduction in oedema
 - Removal of wound exudate
 - Stimulation of granulation tissue formation
 - Decrease in bacterial colonization
- } Secondary to the direct removal of fluid from the wound that induces an interstitial fluid gradient shift.

It is required a systematic analysis of the mechanism of action of NPWT to standardize its use in the clinical practice(9), but effectiveness and cost-efficiency are two constants extensively documented in numerous controlled randomized studies(11).

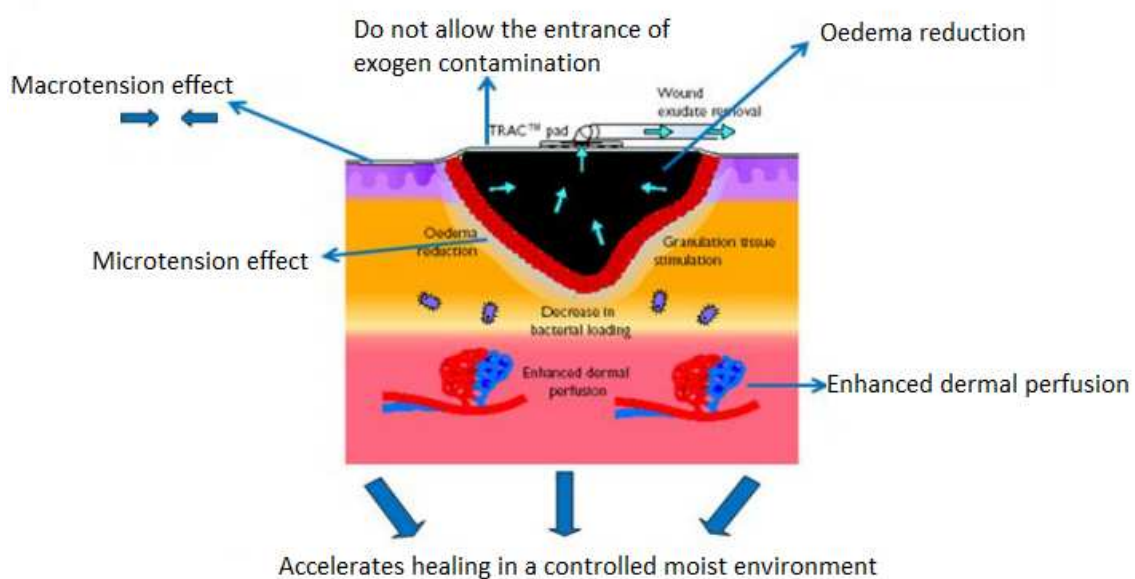


Figure 5. Functionality of VAC® system (11)

Spectrum of TNP effects

TNP is able to modulate the balance between internal cytoskeletal forces and extracellular matrix (ECM) forces which are critical for the control of cell shape, migration, differentiation and tissue patterning.

1. Interstitial fluid flow and exudate management

TNP removes fluid from the wound what induces an interstitial fluid gradient shift that contributes to:

- Reduction in oedema
- Secondary increase in dermal perfusion
- Removal of wound fluid

Oedema reduction

Oedema happen secondary to the effects of the humoral and cellular inflammatory response. → ↑fluid accumulation + ↓interstitial flow within the wound ECM.

NPWT creates an interstitial fluid gradient that removes proinflammatory mediators which contributes to oedema formation. Sceptics argue that the effect is purely anecdotal. However, there is no evidence to demonstrate it.

Wound perfusion

The vascular biology of wounds is complex and not fully understood yet.

Effects:

- Decompress small blood vessels
- Mechanical forces on the extracellular matrix (ECM) will affect the microvasculature. Therefore mechanical stress may be the principal effector.

Wound fluid and proteases

Chronic wounds:

- ↑proteolytic activity generating vitronectin and tenascin-C
- ↑collagenolytic activity to heal open dermal wounds or skin-graft donor sites

Acute wounds:

- ↑proteolytic enzymes + cytokines

NPWT has shown to attenuate tissue damage and physically remove the contrast agent from tissues.

Effect on cellular activity

Reduce the inflammatory infiltrate both in acute and chronic wounds.

2. Mechanical stress

Equally distributed mechanical forces across the wound contributes to angiogenesis

Growth factors and cytokine expression

TNP up-regulate growth factor expression

Granulation tissue formation

Negative pressure allows a macroscopic granulation tissue formation.

Reverse tissue expansion / Macrotension effect⁽¹¹⁾

TNP utilizes the natural visco-elastic forces of the skin adjacent to the open wounds producing a mechanical stretch that increase vascularity of the skin and mitotic activity.

3. Tissue salvage

TNP keeps the wound tissue in the zones of trauma. It removes toxic and pro-inflammatory factors, reducing this way the oedema and inhibiting progression to a deteriorating wound environment.

Bioburden effects

Significant reduction in the wound bioburden has been demonstrated

Moist wound environment

Moist environment provides the optimal conditions for:

- Epithelialization, prevention of tissue dissection, angiogenesis, enhanced cellular metabolism and maintains wound temperature, which is critical for optimal enzymatic processes.

Clinical indications

Clinical indications and contraindications for using this therapy are constantly evolving.

1. Acute wounds

Trauma

Sealed environment:

- Minimishes contamination
- Maximizes oxigenation of tissues by improving local blood flow
- Stimulates granulation tissue via mechanical stress.

Exposed bone, tendon and neurovascular bundles are rapidly envolved with granulation tissue. "Early wound debridement and coverage of exposed bone with well-vascularised tissue, within 72 hours remains the "gold standard" management of open fractures"(9). However, long-term studies are expected for the practice of delayed soft tissue cover..

Complex soft tissue injuries in absence of exposed bone

Once granulation tissue is formed, graft or flap cover is done with good results

Burns

Specially usefull in unstable patients where definitive coverage may be delayed.

2. Surgical wounds

Open abdomen injuries

They are associated with morbimortality higher to 25% and require prolonged hospitalization or laparostomy secondary to dehiscence. They are difficult and expensive to resolve.

- *Long term aftermath:* enterocutaneous fistula formation, ventral hernia development, unstable wounds liable to breakdown and aesthetic considerations
- *Function of VAC® in open abdomen injuries:*
 - Wound control, containing abdominal contents
 - Prevention of infection
 - Wound closure without hernia formation (facilitates fascial closure)
 - Removes exudate and provides quantitative analysis of third space fluid losses

Cardiac wound infection

Reduces the significant incidence of infection poststernotomy with posterior healing through secondary intent or with delayed definitive flap closure.

Despite that TNP is not always recommended, VAC®advantatges are numerous:

- Significantly fewer dressing changes
- Fewer final flap procedures
- Reduction on hospital stays
- Improve ventilation
- Reduction of pain

Skin-graft fixation and donor site complications

VAC®advantatges:

- Firm fixation of a skin graft to its bed following the wound contour.
- Eliminating shearing
- Removing fluid collection
- Inhibiting infection

Graft survival rate with this technique: >90%

3. Chronic wounds

Pressure ulcers

Comorbidity common in the elderly and infirmed patients and those suffering from debilitating neurological diseases. Often reconstructive surgery is required.

NPT properties:

- Effective and safe
- Definitive treatment of pelvic and trochanteric pressure ulcers → less hospital admissions
- Prepares the ulcerated area for surgical intervention

Complex diabetic wounds

TNP is more effective than traditional dressings in managing diabetic ulcers:

- Less nursing demands
- Cost-effective
- Comfort for the patient
- Better outcome

Vascular ulcers

Useful in large venous ulcers, but no in arterial ulcers and those with significant arterial deficiency and persistent local ischaemia (ischaemic human limbs show no improvement in skin microcirculation during or after NPWT)

Clinical contraindications

Absolute contraindications to TNP use are not still established. However, there are some relative ones:

- Over necrotic tissue
- Over open joints
- Over tumour (except from palliative wound care)
- Coagulopathy
- Over open peritoneal or pleural space → interposed dressings are mandatory to minimise damage to underlying structures

Complications

Clinical complications of the use of NPT are listed in **Table 7**.

Complications
Dressing sensitivity
Pain
Pressure necrosis on skin
Haemorrhage
Haematoma
Infection
Toxic shock
Failure of wound to respond
Psychological intolerance

Table 7. Clinical complications of NPT use

There are different units, dressings, canister and accessories of VAC® therapy depending on the clinical indication and the characteristics of the lesion(12). For the realization of this study we are going to use VAC Ulta® for VAC VeraFlo™ instillation technique with Clindamycin and Physiological Saline solution (Clindamycin concentration will depend on the severity and the area affected). Canister will have a capacity of 500 or 1000 mL depending on the size of the surgical incision.

VAC Ulta™

Many acute, chronic and infected wounds can benefit from the supply solutions and automated drain cycles through vacuum cycles and instillation, so it is a double therapy:

- Automated supply of fluid to the instillation of the infected wound
- Homogeneous distribution of fluid instillation using VAC and WhiteFoam in the infected wound
- Elimination of intermittent fluid instillation used helps to clean and drain the wound bed and to eliminate infectious material.
- Provides a closed and moist environment for healing

VAC VeraFlo™ allow total distribution and removal of topical wound solutions across the wound bed and helps to distribute negative pressure evenly. Its accessories images are available in **Figure 6**:

- **TRAC™ Pad:** Provides delivery and removal of wound care solutions
- **VAC VeraTRAC Duo Tubing Set:** Separate delivery and removal pads help enhance fluid circulation
- **VAC Veralink™ Cassette:** Disposable component connects the V.A.C.Ulta™ Therapy Unit to the dressing tubing and to the user-provided solution bag/bottle to provide convenient solution storage and delivery



Figure 6. VAC device and accessories required in this clinical trial(12)

VAC® system utilization

The application of VAC® device is explained in the following figure (Figure 7)

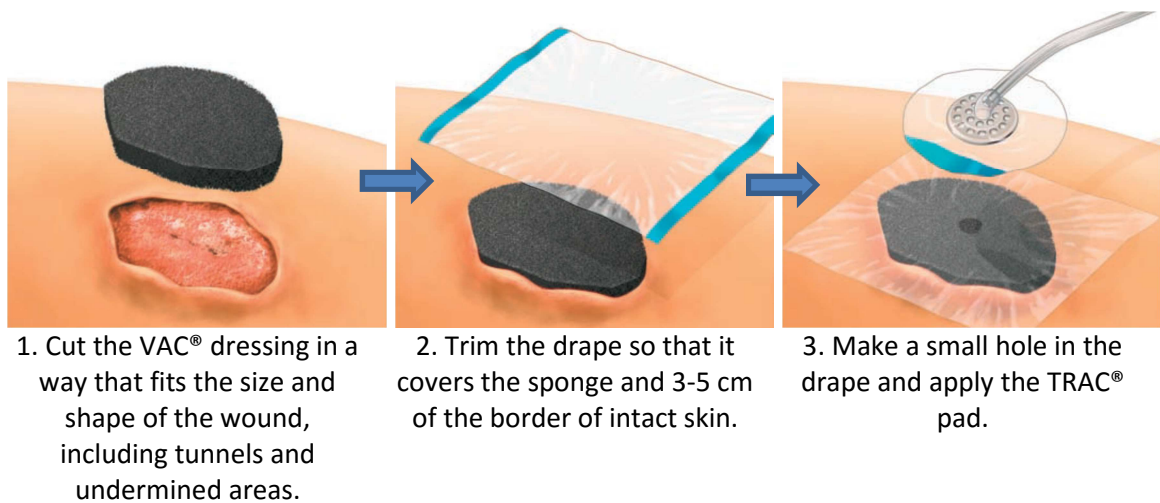


Figure 7. Instructions to the application of VAC®

3.3 NPWT IN PATIENTS WITH HS

NPWT in HS is useful to:

- Stimulate angiogenesis
- Remove interstitial fluid and bacteria
- Promote granulation tissue

The use of NPWT for 5-7days on open wound created after wide debridement of the area affected of HS may be useful in order to remove residual infections, provide drainage and improve perfusion before graft or flap application. It promotes healing, enhances patient comfort and minimizes nursing care. (13)

This procedure has already been studied but never in a prospective way such as a clinical trial.

In 2001, Elwood and Bolitho et al(14) described 2 cases of patients suffering from axillar bilateral HS treated with NPWT in order to get graft succeed. Outcomes were excellent both in acceptance and skin graft take.

In October 2011, Chen and Friedman et al (15) described a case series of 11 patients with 24 regional diseased areas treated with excision followed by NPWT and then skin grafting with the use of NPWT to promote grafts on the site. Only 3 patients required re-grafting and all patients resolved their local diseases.

In May 2014, Chen and Gerstle et al (16) did a retrospective study of 60 HS cases in 27 patients. 30 cases in 12 patients received the same technique as in this article explained above, while 30 cases in 15 patients were performed without VAC®. The healing time between the 2 groups was not significantly different, but outcomes were promising for those patients receiving VAC® therapy with no recurrence of their local disease and they had wounds 4 times larger than the control group

4. JUSTIFICATION

There are several reasons that emphasize the importance of accomplish this study. We are talking about a disease that affects about 1% of the adult European population. Despite of this, HS is considered a neglected disease by healthcare professionals, family, friends and society in general(3).

These people suffer a very upsetting and annoying clinic. Patients suffering from HS present painful inflammation with chronic pain; the purulent discharge from multiple sinuses is accompanied by stained clothing and foul-smelling. This contributes to a limitation on the physical activity (it could be considered a disability) and social stigma with isolation and loss of employment(16). Sexual functioning can also be affected because of perineal involvement and embarrassment.

HS is considered as one dermatologic illness that affects more the QoL (6). Those patients with HS in secondary care score 11.3 in the Dermatology Life Quality Index (17). It has also been identified an elevation of the rate of depression and anxiety disorders on these patients(3).

All medical treatments studied so far have not been successful enough for achieving healing on severe and recurrent cases; this is the reason why we propose a surgical measure. The most accepted surgical procedure for sever stages of HS is radical excision and grafting in the same surgical time; but its relapse rate is 27% in 20 months(8) (much more efficient than medical treatment, but still a high rate of relapse).

The procedure that we want to study consists on a first surgical intervention when the wide debridement of the affected area of HS and VAC[®] therapy implementation will be realized. After 5 days of hospitalization, VAC[®] device will be removed to operate the patient for a second time realizing a skin graft or flap (previously valorated depending on his evolution and the area affected).

We assume that more days of hospitalization are required to do this new procedure, but we prioritize the clinic stable in the patient contributing to a reduction of reinfection rate and consequently also a decrease in the reoperation rate.

The procedure designed proposes using NPWT during five days after the wide debridement and before the grafting in order to guarantee a cleaner wound. It seems logical that in this way the reinfection rate will be lower. In fact, as we have explained in the introduction section ([see 3.3: NPWT in patients with HS](#)), there are three previous studies evaluating a very similar technique(14)(15)(16). All of them have obtained positive results, but they do a retrospective analysis of the dates with too small sample size. No clinical trial has been realized until the moment. That is the reason why we consider that this study has to be performed.

5. HYPOTHESIS

Treatment of radical excision combined with the use of negative pressure wound therapy with posterior skin grafting or flapping achieves a decrease in the number of recurrences in surgical patients of hidradenitis suppurativa in comparison with the radical excision alone.

6. OBJECTIVE

6.1 MAIN OBJECTIVE

To assess the efficacy of a technique that combines current procedures with the use of NPWT with skin grafting or flapping in a second surgical time compared with the current procedures to decrease the number of recurrences in HS patients with stage III or II where conservative treatment has failed.

6.2 SECONDARY OBJECTIVES

- To assess an improvement in the quality of life of patients treated with a technique that combines current procedures with the use of NPWT with skin grafting or flapping in a second surgical time compared with the current procedures in HS patients with stage III or II where conservative treatment has failed.
- To assess the efficacy in healing rate, reoperation rate and adverse events emergence of a technique that combines current procedures with the use of NPWT with skin grafting or flapping in a second surgical time compared with the current procedures in HS patients with stage III or II where conservative treatment has failed.
- To establish the cost-effectiveness about the public costs of chronic patients diagnosed of HS about a technique that combines current procedures with the use of NPWT with skin grafting or flapping in a second surgical time compared with the current procedures in HS patients with stage III or II where conservative treatment has failed.

7. SUBJECTS AND METHODS

7.1 STUDY DESIGN

A randomized controlled clinical trial will be carried out. This clinical trial will be controlled, randomized and unicentric. Patients from Hospital Sta Caterina, Fundació Hospital d'Olot and Hospital de Palamós will be derived to the center of reference of the province of Girona: Hospital Universitari Dr. Josep Trueta, where the study will be made. The duration of this study will take 6 years.

- **Randomization methods**

In order to avoid the selection bias, all patients included in the study will be assigned in a group randomly using a computer with de SPSS software by an external researcher. The investigator will not have access to the randomization sequence and he will not be aware of what techniques belong to any patient. Randomization will be done using a covariate adaptive randomization where a new patient is sequentially assigned to a particular treatment group by taking into account the previous assignments of participants. We have to work in this way because we don't know all the patients of the study before starting it.

Once the randomization is done, information will be transmitted to the surgeon when the patient is in the operation room by receiving a closed envelope the same day of the intervention.

- **Masking techniques**

In this study we will have a detection bias, because there is a lack of blindness. Although the surgeon cannot be a blind investigator, his patients will be properly randomized and he won't know the technique he is going to use until the last moment.

Patients are not blind neither because the postoperative is different depending on the technique used.

There would be one possible solution to avoid this failure: an external evaluator who does not know the technique used (an internal medicine doctor, a dermatologist or a general surgeon) could appraise the reappearances of relapses. But nonetheless, we cannot be sure that the patient will inform this external evaluator of what procedure has been carried out. That's the reason why we have decided that the relapses will be evaluated by the same person that has made the intervention.

To minimize the bias of simple blind, the statistical consultant will not know what treatment each patient has received, so he/she will be masked.

7.2 POPULATION OF INTEREST

Our population will be composed by those patients who are suffering from HS stage III or stage II and in those who conservative treatment has failed.

As inclusion criteria we define:

- Patients (men and women) diagnosed of HS stage III or stage II and in those who conservative treatment has failed
- Patients visited at the Hospital Universitari de Girona Dr. Josep Trueta and those ones referred from Hospital de Palamós, Hospital Sta Caterina and Hospital d'Olot
- Participants must be 18 years or older
- Patients have to understand and sign an informed consent form; otherwise they will not be included

As exclusion criteria:

- Morbid obesity patients [Body Mass Index (BMI) greater than 40]
- Oncologic patients
- Irradiated area affected by radiotherapy
- Life expectancy < 1 year (judged by the surgeon)
- Coagulopathy or bleeding disorder
- Anesthetic risk too high to be involved
- Pregnancy

Despite the fact that smoking, obesity, metabolic syndrome, hypertension, (among others) are known potential risk factors to present the illness in a severe stage,(3) we have decided not to exclude them from the study.

As **withdrawal criteria**:

- Patient is not willing to comply with the protocol
- Medical reasons (adverse event) under investigator criteria
- Participant signs the revocation of information consent (**Annex 3**) not to continue in the study.

Subjects withdrawn from the trial will not be replaced and will be included in the statistical analysis.

7.3 SAMPLING

The sampling system will be consecutive. Every patient visited in our department or referred to us from the centers mentioned before and that fulfill the criteria of inclusion and not exclusion will be enrolled in this clinical trial.

- SAMPLE SIZE

As seen in most of the studies previously made, such as Ritz(8), and based on the clinical experience of plastic surgeons at the Hospital Universitari de Girona Dr Josep Trueta, we estimate that the incidence of recurrence in patients treated with a surgical radical excision is 27%. Therefore, assuming an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, we need 49 patients in each group to detect a minimum relative risk of 0.14 if the tax of the non-exposed group is 0.27 in order to achieve half of the relapses compared with the gold standard technique as minimum. We have estimated that the tax of follow up loses will be 10%, taking into account those patients that will not come to the follow up visits or die during the study. Sample size has been calculated using the approach of POISSON through the "Calculadora de Grandària Mostral GRANMO"(18).

Acknowledging the incidence of HS stage III at the Hospital Universitari de Girona Dr Josep Trueta which is around 25 cases per year we will need at least 5 years to reach the sample size.

7.4 STUDY INTERVENTIONS

Before the intervention patients will have to have an anesthesiologist evaluation in order to determine what kind of anesthesia they will need. Depending on the location and the extension of the affected area general or epidural anesthesia will be considered. Usually general anesthesia is used to sub mammary and axillar affectation and epidural is used to perineal and sacral affectation. But if the area is very infected, physicians may consider a better option to give general anesthesia in perineal zone affectation.

In this study we are going to perform two different surgical procedures to treat HS: radical excision with THPN implantation plus a second intervention five days later to do the skin grafting or flapping and the conventional radical excision with skin grafting or flapping at the same surgical time and.

The procedures will be performed in the operating room of Hospital Josep Trueta de Girona. The material required for the interventions is: plastic surgeon box, electric scalpel, aspirator, gauzes, compresses, carvings and sterile gloves and gowns.

NPWT device is needed for those patients who will receive the first procedure. We have decided that we are going to use VAC® system because our medical and nurse staff are very experienced using this method. In this trial we have decided to work with VAC® system brand for being the one with more published clinical evidence than any other form of TNP (10) and for being the one used in Hospital Josep Trueta of Girona where the study will be done. Moreover, it is the most common and vastly used in the market and previous studies have been made with it (so, our outcome will be easier to compare with them).

Intervention A:

- **Radical wide excision + THPN implantation + skin grafting/flapping for a second time**

This intervention consists of doing a large debridement of the affected area channeling of sinus tracts and removing them (**Figure 8**). We will extend the resection margin by 0.5cm in order to clean the zone as much as possible. Margins will be sent to pathological anatomy service to make sure that they are free of infected tissue. Whole procedure performance takes about two hours. After the intervention, immobilization with tight-fitting is recommended.

We will place a VAC system and the patient will be hospitalized for five days before the second intervention. As mentioned in the Introduction (**see 3.2: Negative Pressure Wound Therapy**) for the realization of this study we are going to use VAC Ultra® for VAC VeraFlo™ instillation technique with Clindamycin and Physiological Saline solution (Clindamycin concentration will depend on the severity and the area affected). Canister will have a capacity of 500 or 1000 mL depending on the size of the surgical incision. NPWT will diminish the occurrence of infected tissue and will help the creation of granulation tissue. This system needs switching VAC VeraFlo™ fungible part one time on the 3rd day. Once the wound is clean and ready to receive a skin graft/flap, the patient will be operated again. The donator area will be different depending on the zone affected. The plastic surgeon performing the intervention will decide beforehand which is the best way to proceed to get the best results. This time the postoperative period is expected to be of four days, depending on the evolution of the patient.

During the hospitalization the doctors and nurses of the team will record the patient evolution in the Participant Data Sheet (**Annex 5**).

Intervention B:

- **Radical wide excision + skin grafting/flapping at the same surgical time**

The difference from the intervention previously described remains on the fact that skin grafting or flapping will be done in the same surgical time.

After this intervention the patient will be admitted into the plastic surgery ward for four days, at least, to make sure the success of the graft. During the hospitalization the doctors and nurses of the team will record the patient evolution in the Participant Data Sheet (**Annex 5**).

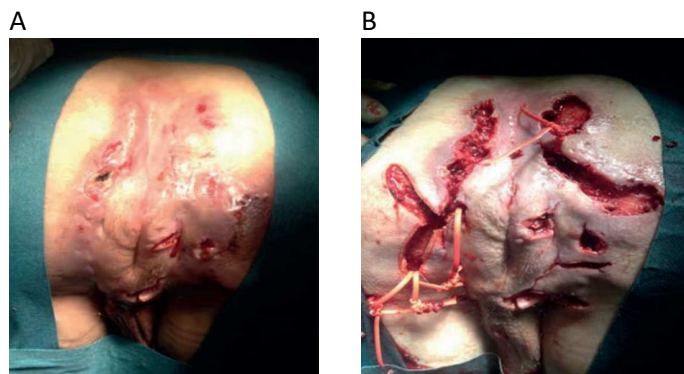


Figure 8. (A) It is visible the perineal area affected of HS in stage III of Hurley and **(B)** its result after surgical treatment of wide radical excision. At this point, VAC® implementation would be realized in intervention A and skin grafting or flapping would be done in intervention B. Images from 'Tratamiento quirúrgico de la Enfermedad de Verneuil o hidrosadenitis severa'(19)

7.5 VARIABLES

Every measure or data will be collected at the Hospital Universitari de Girona Dr Josep Trueta, where the patients will be seen, treated and followed up.

- **Independent variable**

The independent variable of this study is the allotment of one of the two surgical treatments: radical excision with or without the posterior use of VAC ([see 7.4: Study Interventions](#)). It is considered as a dichotomous qualitative variable.

- **Dependent variable**

The primary variable of the study is the relapse rate that occurs 20 months after the surgical intervention. The relapse is defined as a recurrence of the illness in any stage in the same location of the previous surgical area. If there is no relapse we will define our treatment as a success and we will consider that the patient is cured. This is also a dichotomous qualitative variable, so the information of the patients will be collected in an anonymous way on a table named as “patient with relapse” and “patient without relapse”

Secondary variables

All secondary variables will be evaluated by one plastic surgeon of the research team during outpatient visits. The information collected will be written in the Participant Data Sheet ([Annex 5](#))

- **Quality of Life (QoL):** is a qualitative variable that will be evaluated using the Dermatology Life Quality Index (DLQI) ([Annex 6](#)).
- **Cure rate:** is a dichotomous qualitative variable assessed during the outpatient visits. All patients with no relapses in the 20 months of evaluation will be considered cured.
- **Reoperation rate:** is a discrete numerical quantitative variable based on dates collected during the elaboration of this trial. Those patients who requiring a reintervention will be included for the statistical analysis of reoperation rate.
- **Appearance of adverse events:** is a qualitative variable. Every adverse event described by the patient will be collected in the Participant Data Sheet ([Annex 5](#)).
- **Success of the graft:** is a dichotomous qualitative variable, so the information collected will be collected in a table named as “graft success” and “graft failure”.
- **Public costs:** discrete numerical quantitative variable that will be useful to demonstrate the cost-effectiveness of the treatment. Public costs will be collected and valued to balance costs and benefices.

Covariates

Covariates are summarized in the following table (**Table 7**):

Covariates	Characteristics of the variable	Measurement unit	Risk factor known
Gender	Dichotomous nominal qualitative	Male / Female	Women
Age	Discrete quantitative	Years	Puberty
BMI	Continuous quantitative	kg/m ²	>25 kg/m ²
Genetic alterations	Dichotomous nominal qualitative	Yes/No	Gamma-secretase enzyme mutations
Pack-year smoking	Dichotomous nominal qualitative	Smoker / Not smoker	Smoker
Tight clothes	Dichotomous nominal qualitative	Yes / No	Yes
Deodorants	Dichotomous nominal qualitative	Yes / No	Yes
Waxing products	Dichotomous nominal qualitative	Yes / No	Yes
Drugs	Nominal qualitative	Name of the drug and dosage	Oral contraceptives and lithium
Duration of symptoms	Continuous quantitative	Weeks Pain will be assessed through the score of Dermatology Life Quality Index (DLQI) (Annex 6)	

Table 7. Description of covariates in this clinical trial. All the information collected by the patient will be written in the Participant Data Sheet (**Annex 5**) except from genetic alterations, because it is not our principle objective of the work and it would generate higher costs.

7.6 DATA COLLECTION

Baseline

The first visit will be held at the outpatient service at Hospital d'Olot, Hospital Sta Caterina, Hospital de Palamós or Hospital Josep Trueta de Girona. If patients go to the top three hospitals mentioned, physicians of the service will derivate these patients to Hospital Josep Trueta de Girona.

The main objective of this visit will be to diagnose HS disease and establish its degree and if there is surgical indication. To be able to determine this, a complete anamnesis and physical exploration is needed. It will be important to collect the general demographic data: demographics, personal and family history, regular medication taken, steroid use, immunosuppression, surgical area and some habits that are risk factors such as tobacco consumption, wearing tight clothes, using waxing products in the affected area or use of

deodorants. A nurse will record some basic data exploration such as: height and weight (stadiometer) to calculate the BMI; blood pressure and heart rate (tensiometer, Omron®). Despite the fact that there are some genetic alterations associated with the illness, we will not register them in our study because it is not our main objective and the costs would increase too much.

If our patient meets the criteria of inclusion and nor the exclusion ones, we will propose the patient to participate in our study. Once the patient agrees to enter the trial, it will be necessary to sign the Information Sheet (**Annex 1**) and the written Informed Consent (**Annex 2**). It is then when a numeric code is allocated to the patient to be able to implement the randomization.

Preoperative assessment

Before the intervention, an anesthesiologist will do a preoperative evaluation. This procedure includes scoring from the ASA classification.

Hospital admission and surgical preparation

Patients will be admitted to hospital 12 hours before the intervention in order to check their vital signs. Floor nurses will measure temperature, take blood pressure and heart rate. It is very important that the patient does not eat or drink anything 6 hours before the surgery.

The affected area of HS must be shaved off in order to perform the surgery.

Study Intervention

Just before the intervention, the surgeon will receive a closed envelop prepared by the statistician that contains the surgical procedure that he must follow.

This procedure will be performed by surgeons, instrumentalist nurses and anesthesiologist in the operating room.

Total procedure time (from skin incision to closure or placement of VAC system) should be registered, as well as complications during the procedure. It is estimated that this procedure will take at least two hours.

Postoperative assessments

After the intervention patients will go to the post-surgical unit until they recover from anesthesia. It is suspected that this period will take approximately 4 hours. After the recovery the patient will return to the plastic unit.

Depending on the procedure that the patient has had, the discharge time will be different. Patients receiving the conventional procedure will go home in 4 days (depending on their evolution). Patients receiving the VAC procedure will have a second operation 5 days after the first one, having to stay in hospital for another 4 days

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Plastic surgeons will visit patients every day to evaluate their evolution and the possibility of relapses. Nurses will also record the need of extra-analgesia (pain assessment, VAS), temperature, blood pressure and liquid extracted from the radon which will be very important to assess the patient's progress.

Visity

The main objective in our study is to detect short and long term relapses of the illness. We will evaluate this during the visits that will take place in the outpatient service in weeks 2, 4, 12, 24, 48 and 80 and collect the information in the Participant Data Sheet ([Annex 5](#)). If a relapse/complication appears after the intervention, the patient can make an appointment at any moment.

The physician will take advantage of the visit of weeks 4, 24 and 80 to ask for patient's satisfaction filling the Questionnaire of Quality of Life ([Annex 6](#)).

7.7 SCHEDULE OF ASSESSMENT

Hour (h), Days (d), Week (w)	-2d	-12h		1d	2d	3d	4d	5d	6d	7d	8d	9d	2w	4w	12w	24w	48w	80w
Visit (V)	-3	-2	-1	0	0			0					1	2	3	4	5	6
First visit [Outpatient service]																		
Anamnesis + Physical exploration Diagnosis & degree of HS Fill in "Participant data sheet"+"Information sheet"+"Informed consent" Allocated a numeric code																		
Preoperative [Anesthesiologist service]																		
Preoperative evaluation ASA classification																		
Hospital admission and surgical preparation [Plastic surgery floor]																		
Check vital signs Not eat or drink 6h before the surgery + Shave off the surgical area																		
Procedure B: Intervention [Operating room]																		
Randomization Radical wide excision + skin grafting/flapping Register total procedure time and complications																		
Procedure B: Postoperative [Post-surgical unit + Plastic surgery floor]																		
Recover from anesthesia (4h) + Check vital signs and complications Record extra-analgesia, temperature, blood pressure and liquid extracted from the radon																		
Procedure A: 1st Intervention [Operating room]																		
Randomization Radical wide excision + VAC implantation Register total procedure time and complications																		
Procedure A: 1st Postoperative [Post-surgical unit + Plastic surgery floor]																		
Recover from anesthesia (4h) + Check vital signs and complications Record extra-analgesia, temperature, blood pressure and liquid extracted from the radon																		
Procedure A: 2nd Intervention [Operating room]																		
Skin grafting/flapping Register total procedure time and complications																		
Procedure A: 2nd Postoperative [Post-surgical unit + Plastic surgery floor]																		
Recover from anesthesia Check vital signs and complications Record extra-analgesia, temperature, blood pressure and liquid extracted from the radon																		
Visity [Outpatient service]																		
Short & long term relapses (Record in participant data sheet)																		
Fill in Questionnaire of Quality of Life																		

8. STATISTICAL ANALYSIS

Sample size calculation has been described in subjects and methods section (see 7.3: Sampling). Statistical analysis will be held with Statistical Package for the Social Sciences (SPSS) software for Windows®.

Univariate

The results will be shown as percentages for categorical variables, while the univariate analysis of the quantitative variables will be represented by mean of \pm SD if we can assume a normal distribution or if not, using the median, first and third quartile.

Bivariate

The Relative Risk (RR) with a confidence interval of 95% will be calculated for each group to analyze our primary objective.

To prove statistical association between gender, genetic alterations, pack-year smoking, deodorants, waxing products and the presence of HS, χ^2 (Chi Square) test will be required.

For analyzing BMI and duration of symptoms, statistical analysis will be realized using a t-student.

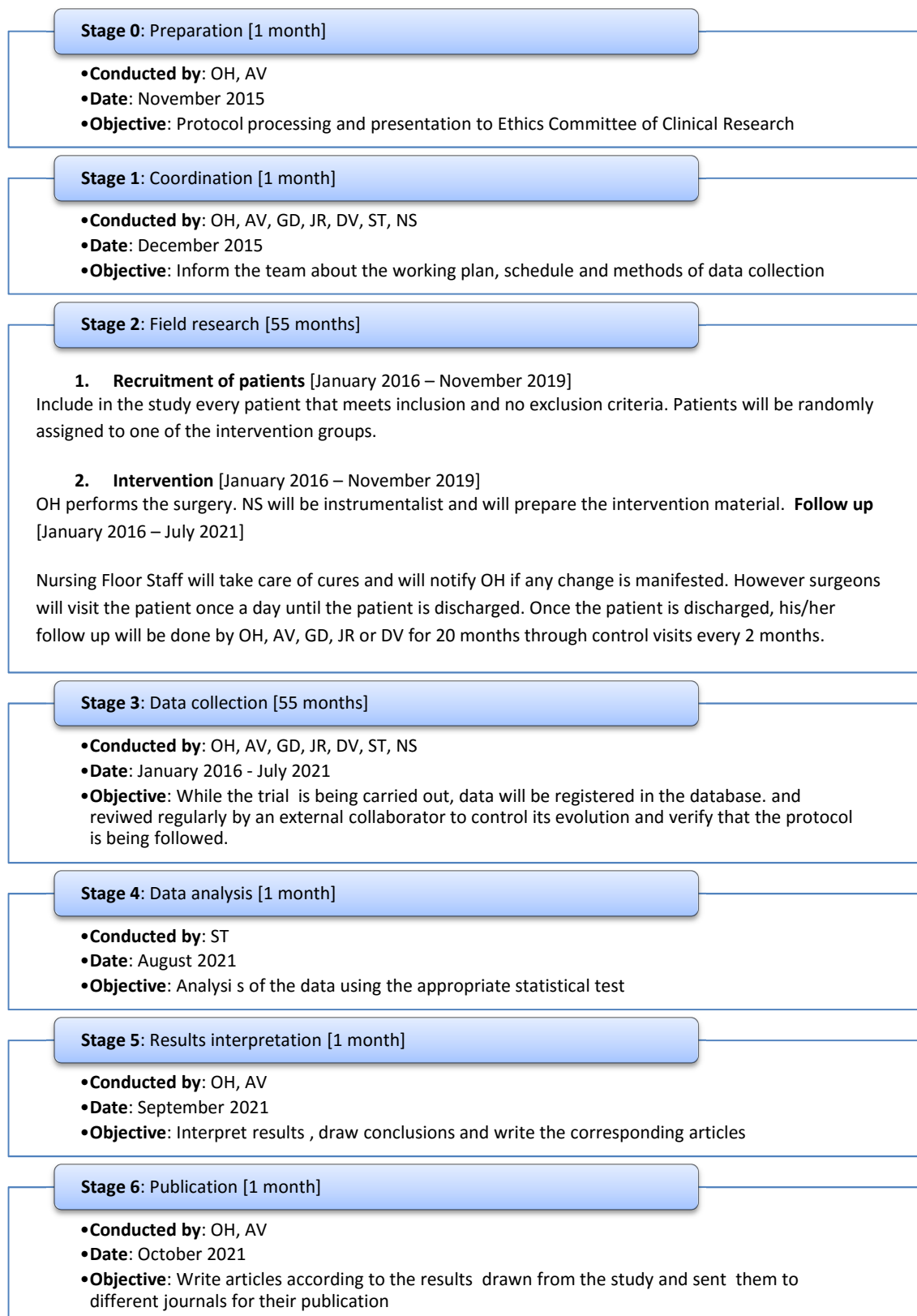
Multivariate

Moreover, multivariate logistic regression analysis will be performed in order to appraise the contribution of the covariates or possible confusion variables in the results such as age or tobacco consumption. It will be made using logistic regression model. We will assume a confidence interval of 95% and P value <0.05 to consider that there is a significance difference.

9. WORK PLAN

Researchers: Dr. Oscar Huc (OH), Andrea Ventura (AV)

Collaborators: Dra. Glòria Dargallo (GD), Josep Maria Ribes (JR), David Valero (DV), Nursing Staff (NS)



9.1 CHRONOGRAM

Year Months	2015		2016	2017	2018	2019		2020	2021			
	XI	XII	I - XII	I - XII	I - XII	I - XI	XII	I - XII	I - VII	VIII	IX	X
0. Preparation phase [OH, AV]												
1. Coordination phase [OH, AV, GD, JR, DV, ST, NS]												
2. Field research [OH, AV, GD, JR, DV, ST, NS]												
<i>Recruitment of patients</i>												
<i>Intervention</i>												
<i>Follow up</i>												
3. Data collection [OH, AV, GD, JR, DV, ST, NS]												
4. Data analysis [ST]												
5. Results interpretation [OH, AV]												
6. Publication [OH, AV]												

10. ETHICAL AND LEGAL ASPECTS

The most important thing whilst carrying on this study, is to respect the ethical principles that characterize a good clinical practice. In accordance with provisions of the organic law 15/1999 of the 13th of December about data protection, confidentiality and protection of personal data shall be guaranteed. All information obtained during the trial will be treated in an homogenous way during the data collection process.

All participants will be informed about the interventions and the details of this clinical trial. They will be given an Information Sheet (**Annex 1**), Informed Consent for the Inclusion in the Study (**Annex 2**) and an specific Informed Consent to have the Surgical Intervention (**Annex 3**). It is imperative that patients read and understand the information sheet and sign the informed consent forms too. Thereby, the principle of autonomy will be respected.

In this clinical trial the right of health protection will be respected as per article 43 of the Spanish Constitution of 1978. Patients have the right to leave the trial at any time with no impact on the health care they receive. All patients will be insured for harm and damages that might result from the investigation.

As regulated by the law 14/2007 of the 3rd of July about biomedical investigation, this trial will have to be approved by the Clinical Research Ethics Committee (CEIC) of the Hospital Universitari Josep Trueta of Girona and it will be registered in ClinicalTrials.gov and in EudraCT.

This trial will follow the Spanish drugs and health products law (Real Decreto 1591/2009 de 16 de octubre y 1616/2009 de 26 de octubre: Investigación con Productos Sanitarios).

The principles of human experimentation are equally respected as provided by the Helsinki agreement.

The few trials done with this technique have been satisfactory; for this reason, our study does not involve many ethical problems, some ethical dilemmas have appeared whilst carrying this study. Current surgical techniques have a high relapse rate, but the healing method that we are raising implies more time in hospital. We have hypothesized that making a wider debridement using VAC, the number of relapses decrease. The higher probability of overcoming the illness solves the dilemma.

There is a conflict with regards to the patients that receive the current surgical treatment for HS when in reality, we think that the new method is better. As our hypothesis is not yet proven, patients who receive the classical treatment (which has the greatest scientific evidence), are not being subjected to a worse intervention, so we are not violating any ethical aspect.

11. STRENGTHS AND LIMITATIONS

In “masking techniques” section (see 7.1: Study design) we have explained that in this trial there is a detection bias because it is not possible to make a triple blinding. In order to solve this limitation we are going to take some measures: surgeon will not know which procedure is going to perform until just before starting the surgery and the statistician will be blind, he/she will always work with patient’s codes and will not know at any moment the intervention received for each of them. An external evaluator checking the relapses appearance would be a good solution to avoid the lack of blindness of the physician. But even so, as patients are receiving a different postoperative depending on the technique realized, they would be able to say to this external evaluator which procedure has been performed to them. That is the reason why we have decided that the relapses will be evaluated by a plastic surgeon of the team.

As we are carrying out a study about a surgical intervention that will be performed by four different surgeons, a procedure bias can be present. Operator experience is one of the keys to technical success. In order to solve this mishap we are going to meet us during the coordination phase of the study to define the details of the surgical intervention to be able to work in a very similar way. Anyway, all surgeons in the team have had comparable formation are used to work with such analogous procedures.

Secondary variables proposed in the protocol will be valued, but they will not have a definitive result because of the sample size or other methodological differences. To be able to extract conclusions of the data collected; new protocols to investigate these variables should be created. Moreover, it will be very interesting having a Questionnaire of Quality of Life validated that fit exactly our goal.

It will be important to control all the covariables known by the moment to distribute the most risky patients symmetrically in both groups of the intervention. This way the information will be extrapolable to Girona’s population, but not necessary to other populations.

Losses or withdrawals during the study realization may behave a follow up bias. All the reasons why the patient has decided to withdraw of the study will be described in the outcomes of the project and their dates will be included into the statistical analysis as they have not had emergence of relapses.

Due to the low incidence of the severe cases of HS in Girona’s province, five years are necessary to collect the sample. Maybe it would be a good idea considering a multicenter study to solve the long duration of our protocol, but there would be more variability on the performance of the surgery and the realization would be more difficult and expensive.

12. FEASIBILITY

Medical team

In this clinical trial we will have a multidisciplinary team. The main investigator will always be the same surgeon: Oscar Huc. He is the chief of plastic surgery at the Hospital Universitari Dr. Josep Trueta of Girona and he is very experienced in the surgical treatment of HS and in the use of NPWT for other conditions.

Nursing staff will be the usual nurses that are used for this surgery and that have been many years working with surgeon Oscar Huc. Floor staff nurses are also accustomed to work with VAC and will have specific training on how to use this machine.

This surgical team has not got enough knowledge to do an extensive statistical analysis, that's why we are going to hire an external statistician.

All workers will be hired by the National Health System.

Available Resources

The operation room is available two days per week with all the instruments except for the NPWT. There are 10 VACs accessible in the hospital, so before any intervention we have to make sure that they are free and obtain the fungible part of the instrument. We will have to take into account that patients receiving current treatment of HS will have to rest in hospital for 4 days after the intervention; while patients receiving the treatment combined with VAC will have to rest 9 days. Therefore it is important to have enough available beds for these patients.

The material required for this trial is:

- Plastic surgeons box, electric scalpel, aspirator, gauzes, compresses, carvings and sterile gloves and gowns

Patients

Assuming referral of patients from Hospital Sta Caterina, Fundació Hospital d'Olot, Hospital de Palamós and our own patients from Hospital Universitari Dr. Josep Trueta; we approximate an inclusion in the study of 25 patients per year. The evaluation of the relapses will be done 20 months after the intervention as the latest. Thus 55 months will be necessary to get the sample size and to evaluate the relapses rate.

13. BUDGET

1. Services and material

As the research team is employed by the institution and it is not required to work overtime their services are not included in our budget. A Statistician will be necessary to analyze the results because our team has not enough knowledge to prepare this section. The estimated budget for this is 5600€ (35€/h, assuming 160h).

We also require skilled staff to carry out the data monitoring, quality control data as well as regular submissions to The Spanish Medicine Agency. The estimated budget for the Clinical Research Associate (CRA) is 6720€ (30€ per hour, assuming 1 hour per week per 56 months)

National Health Service provisions include surgical material except for those patients receiving the NPWT alternative treatment (**see Available resources in “Feasibility section”**). VAC® group yields to the hospital 4 VAC Ultra™ unit to carry on the intervention. This means that we just have to pay the fungible part (VAC VeraFlo™) which costs between 70 and 90€ depending on the size, for the 49 patients receiving this procedure. We must take into account that 2 fungible parts will be needed for each patient because on the 3rd day of hospitalization it have to be changed (Aprox. 160€/patient for 49 patients sum 7840€).

Patients treated by the conventional procedure will rest 4 days in hospital, while those receiving the VAC system one will be 9 days in hospital. These extra 5 days are due to the fact that they will need a second intervention. So we will just consider the cost of these 5 days of (1000€/day for 49 patients sums 245000€). Also this second intervention will mean that surgical rights will have to be paid (400€/patient for 49 patients adds up to 19600€)

We assume 30€ cost for printing information sheets for patients, informed consent forms and participant data sheets.

2. Publication and presentation costs

In order to disseminate the information collected with the outcome of our study we will try to publish our clinical trial in scientific journals with open access such as Journal of Plastic Surgery. Publication costs add another 2500€.

Besides this it would be interesting to participate at the “Congreso Nacional de la Sociedad Española de Cirugía Plástica, Reparadora y Estética” in 2022. The location where the congress will take place is still unknown. We have estimated at 350€ the costs of the flight, accommodation and food and the registration fee will cost around 600€.

	Quantity	Cost	Subtotal
1. Services and material			
Statistical expert for data analysis (1)	160h	35€/h	5600€
Clinical Research associate (CRA)	56m x 4h	30€/h	6720€
VAC VeraFlo™ (fungible part)	49	100€	7840€
Hospitalization	49 patients x 5d	1000€/d	245000€
Surgical rights	49	400€	19600€
Printing and paper	1	20€	30€
Insurance policy	1	6000€	6000€
2. Publication and presentation costs			
Inscription to "Congreso Nacional de la Sociedad Española de Cirugía Plástica, Reparadora y Estética" (SECPRE)	1	600€	600€
Flight, accommodation and food	1	350€	350€
Publish in Journal of Plastic Surgery	1	2500€	2500€
TOTAL AMOUNT			294240€

14. IMPACT

As we exposed in the Justification section, it is not a negligible amount of people that suffers from HS. In spite of this it exists an under-recognition of HS by doctors and society in general (3)

It is important to solve the clinics that upset these patients. Our main objective is to abolish the chronic pain and inflammation, the sexual dysfunction and the purulent discharges that stain and stench clothes contributing to social isolation.

Maybe staying five more days hospitalized can seem uncomfortable for the patient and its family. But in the long term, thanks to better results from the intervention and the reduction in the rate of reoperation, they will appreciate it. In the same way we notice a health system impact on the reduction on the rate of hospitalizations and reoperations, what seems to be cost-effective.

If we are able to remove their clinics and eradicate their physical limitations, this amount of people will have best quality of life with fewer cases of depression and anxiety. They will be more productive in their own personal and professional lives.

The importance of this project is that there is no fully effective treatment for HS yet and this procedure seems to be an easily applicable solution. There are only three previous studies about this new technique (14)(15)(16). The three of them have recognized positive results, but they are retrospective studies with too small sample size. This is why this clinical trial is needed to make a step forward in the treatment of this disease. If we get the expected results, we hope that this study will provide more information about this technique to be used widely in the HS treatment.

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16. ANNEXES

ANNEX 1. INFORMATION SHEET

Title: EFFICACY AND SAFETY OF NEGATIVE PRESSURE WOUND THERAPY IN TREATING HIDRADENITIS SUPPURATIVA AND REDUCING ITS RELAPSES: A RANDOMIZED CONTROLLED CLINICAL TRIAL

Investigators: Oscar Huc, Andrea Ventura

Location: Hospital Universitari Josep Trueta de Girona

General information:

We are writing to inform you about an investigation research that is being carried out in this center and which you are invited to participate. We would like you to consider this research study and then decide whether or not you wish to take part in it. It is very important for you to read and understand why the research is being done and what it will involve. Please read the following information carefully and we will clarify any doubts that you might have.

Volunteer participation

Your participation in the study is totally voluntary. You are free to decide whether to participate or not and to withdraw at any time and without any reason. If you decide to take part we will ask you to sign a consent form. Your decision will not affect the healthcare treatment you receive.

You have been chosen because you have been diagnosed with hidradenitis suppurativa and you meet all the inclusion criteria and none of the exclusion ones.

You should also know that you can be excluded from the study if the investigators or the sponsor of the study considers it necessary, whether for reasons of safety (adverse effects caused by the study medication) or because they feel you are not complying with the procedures established. In any case, you will receive a proper explanation of the reason that has led to your withdrawal from the study.

Description of the study

The main objective of this study is to analyze the efficacy and safety of NPWT in treating hidradenitis suppurativa and reducing its relapses. Half of the patients participating in this study will receive the conventional treatment of radical wide excision and skin grafting in one surgical time. This procedure requires just four days of hospitalization. The other half of the patients will be operated with a radical wide excision and, instead of doing the skin grafting in the same surgical time, they will be implemented a VAC system. The patient will rest for five days with this NPWT before being having a

second operation to extract the VAC system and do the skin grafting. This second procedure will require five more days of hospitalization than the first procedure, but we suspect that the results will be better and reduce the relapses rate. Patients will be assigned to one intervention or the other in a randomized way controlled by a statistician.

After the intervention you will be seen by a plastic surgeon in outpatient service for 20 months (exactly in the weeks 1, 4, 12, 24, 48 and 80 after the procedure) when the data collection will finish. If you need extra visits because of any complications or worries that you might have, you can ask for an appointment at any time.

Benefits and risks of participation in the study

Your condition of hidradenitis suppurativa should be treated. If you receive the conventional treatment, you will receive the same treatment as if you do not participate in the study. If you are in the VAC system group you can benefit from better results with less relapses risk, but you will have to rest more days in hospital.

The adverse side effects in both interventions are practically the same: pain, relapses, swelling, erythema, localized bruising, itching and slight bleeding. There is also the possibility of flap or graft failure (what would require a new operation).

Responsibility and insurance

The sponsor of the study has signed an insurance policy that covers any damage you may suffer as a result of your participation in this trial, in accordance with the law.

Confidentiality

All patient data is stored on a password protected computer database. The information will be kept confidential according to current data protection law (Llei Orgànica 15/1999 de "Protecció de Dades de Caràcter Personal").

Records collected during the study will be identified by a numeric code and only the researchers and collaborators will have access to this information. Your identification will never be disclosed.

November 2015

Economic compensation

Your participation in the study will not involve any additional cost. You will not pay for the medication prescribed during this study.

Contact

If there is any doubt or problem during the trial period you can get in touch with the researchers:

Andrea Ventura and Dr. Oscar Huc

Tel: 972940200

Hospital Dr. Josep Trueta. Plastic Surgery Department

Av/ de França, s/n. 17007 – Girona

Thank you for reading this.

Try to keep this information sheet for your records until you finish your participation in the study.

Any queries, questions or doubts, do not hesitate to ask us.

If you decide to participate in the study, sign the consent form below.

November 2015

ANNEX 2. INFORMED CONSENT TO PARTICIPATE IN THE CLINICAL TRIAL named: EFFICACY AND SAFETY OF NEGATIVE PRESSURE WOUND THERAPY IN TREATING HIDRADENITIS SUPPURATIVA AND REDUCING ITS RELAPSES: A RANDOMIZED CONTROLLED CLINICAL TRIAL

- I have been informed by the investigator about the purpose of the study
- I have read and understood the information sheet
- I have had time to think and consider this information
- I have had the opportunity to ask any questions and be answered
- I understand that my participation is entirely voluntary and I can withdraw this study any moment I wish, for any reason and without any consequences for the healthcare I receive.
- I give permission to collect my data and analyze it. I have been informed that all my data will be kept confidential.
- Finally, I agree to participate in this study:

Name of participant

ID

Signature

Name of Doctor taking consent

ID

Signature

Girona, _____ of _____ of 20 _____

ANNEX 3. INFORMED CONSENT TO SURGICAL PROCEDURES

I, _____ have read the information sheet that Dr. _____ has given to me. I have understood everything he/she has explained to me and he/she has answered all my questions. I also understand that, at any time and with no need for an explanation, I can withdraw the consent that I am giving now. That's why I confirm that I feel comfortable with the information that I have received and I understand the nature and risks that can happen during the surgical procedure and also the specific risks that can appear in my case because of my clinical situation and my personal circumstances (personal risks) that are:

In these conditions I give my consent to have the following procedure

Girona, ___/_____/20__

Patient's signature

Doctors's signature

DNI:

Graduate Number

November 2015

REVOCAION OF INFORMATION CONSENT

I, _____ withdraw the consent that I gave on ___/_____/20___. So, after the information received, I declare that I do not give permission to submit me to the surgical intervention: _____

Girona, ___/_____/20__

Patient's signature

Doctor's signature

November 2015

ANNEX 4. RESEARCHER COMMITMENT

Dr./Mr. _____

Service:

Center:

Exposes:

I have evaluated the protocol of this clinical trial titled:

EFFICACY AND SAFETY OF NEGATIVE PRESSURE WOUND THERAPY IN TREATING HIDRADENITIS SUPPURATIVA AND REDUCING ITS RELAPSES: A RANDOMIZED CONTROLLED CLINICAL TRIAL

Referring to these aspects:

- The clinical trial respects the ethical rules relevant to these kind of studies, according to good clinical practice recommendations, in Helsinki, Declaration of World Health Organization (15 January of 2001), and to the legal normative applicable.
- I agree to participate as the main researcher in this clinical trial.
- I have all the material and human resources necessary to carry on the clinical trial without affecting the performance of other studies or my usual duties.
- I compromise to treat and control every patient according to CEIC protocol and authorized by the “Agencia Española de Medicamentos y Productos Sanitarios” (AEMPS)

Signed,

Girona, ____/_____/20__

ANNEX 5. PARTICIPANT DATA SHEET

DEMOGRAPHIC DATA
Patient's code
Name and surnames
Date of birth
Telephone
Email
Sex
Address
Day of first visit
Day of intervention

History
Medical and surgical history
Personal history of HS (surgical site, duration of symptoms, ...)
Family history of HS (members affected and grade)
Allergies
Regular medication (drug name and dosage)
Immunosuppression

HABITS that might be risk factors			
Tobacco consumption (smoker/not smoker/former smoker; packs/year; years smoking)			
Steroid use	Yes	No	
Use of tight clothes	Yes	No	
Use of waxing products	Yes	No	Which ones?
Use of deodorants	Yes	No	

PREOPERATIVE INFORMATION				
ASA classification (American Society of Anesthesiologists)				
I	II	III	IV	V

Procedure performed:

- A:** Radical wide excision + THPN implantation + skin grafting in a second time
- B:** Radical wide excision + skin grafting in the same surgical time

PROCEDURE A:

INTRAOPERATIVE INFORMATION (1 ST INTERVENTION)
Total procedure time (min)
Incidents

POSTOPERATIVE INFORMATION (1 ST INTERVENTION)
Information collected every day during hospitalization
<i>Temperature</i>
<i>Blood pressure</i>
<i>Liquid extracted from radon (mL)</i>
Days until 2nd intervention
Need of extra analgesia
Adaptation to VAC system
Occurrence of complications

INTRAOPERATIVE INFORMATION (2 ND INTERVENTION)
Total procedure time (min)
Incidents

POSTOPERATIVE INFORMATION
Information collected every day during hospitalization
<i>Temperature</i>
<i>Blood pressure</i>
<i>Liquid extracted from radon (mL)</i>
Days until discharge
Need of extra analgesia
Occurrence of complications
General patient satisfaction with the intervention (0-5 where 5 is completely satisfied)
Postoperative groin discomfort or pain (0-5 where 5 is intolerable pain)

PROCEDURE B:

INTRAOPERATIVE INFORMATION
Total procedure time (min)
Incidents

POSTOPERATIVE INFORMATION
Information collected every day during hospitalization
<i>Temperature</i>
<i>Blood pressure</i>
<i>Liquid extracted from radon (mL)</i>
Days until discharge
Need of extra analgesia
Occurrence of complications
General patient satisfaction with the intervention (0-5 where 5 is completely satisfied)
Postoperative groin discomfort or pain (0-5 where 5 is intolerable pain)

PROCEDURE A and B:

OUTPATIENT SERVICE VISITS
Fill in the Safety Data Collection Sheet if any complication or any relapse is detected.
Fill in the Questionnaire of Quality of Life to be able to know the level of satisfaction with the procedure.

SAFETY DATA COLLECTION SHEET

ADVERSE EFFECTS	
Patient's code	
Person recording to database	
Adverse effects	
Start date	
Finish date (in case of resolution)	
Level of Severity	mild/moderate/severe
Criteria of Severity	Dead
	Vital risk
	Hospitalization or extension of hospitalization
	Disability/persistent or important disability
	Important medical event
Actions taken to reverse the adverse effect (if taken)	

ANNEX 6. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: Date:

Name: Score:

Address: Diagnosis:

.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

- | | | |
|---|-------------------------------------|---------------------------------------|
| 1. Over the last week, how itchy, sore, painful or stinging has your skin been? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | |
| 2. Over the last week, how embarrassed or self conscious have you been because of your skin? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | |
| 3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 4. Over the last week, how much has your skin influenced the clothes you wear? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 5. Over the last week, how much has your skin affected any social or leisure activities? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 6. Over the last week, how much has your skin made it difficult for you to do any sport ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 7. Over the last week, has your skin prevented you from working or studying ? | Yes <input type="checkbox"/> | |
| | No <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| If "No", over the last week how much has your skin been a problem at work or studying ? | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | |
| 8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 9. Over the last week, how much has your skin caused any sexual difficulties ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |

Please check you have answered EVERY question. Thank you.

DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life
2 – 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life