SYSTEMATIC REVIEW

The Pathogenesis, Risk Factors, and Comorbidities Associated with Hidradenitis Suppurativa: A Systematic Review

Róisín Guihen[a]*, Jack Latvis[a], Honora MacNamara[a], Emma Quinn[a], Sarah Hennessy[a], Cian Meagher[a], Julie MacMahon[a,b]

[a] *School of Medicine, Trinity College Dublin, University of Dublin, Ireland*
[b] *Department of Dermatology, Tallaght University Hospital, Tallaght, Dublin 24, Ireland*
**Corresponding author: GuihenR@tcd.ie*

Abstract

Introduction: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease primarily affecting the apocrine gland-rich areas of the body. It presents with painful nodules, abscesses, sinus tracts, and scarring.

Methods: A literature review of hidradenitis suppurativa was conducted by systematically searching relevant databases with a focus on the pathogenesis and risk factors associated with the disease.

Results: Evidence relating to pathogenesis and HS thus far supports an inflammatory component with dysregulation of the innate and adaptive immune system. However, research is ongoing in this area and many questions remain unanswered. The risk factors that have been most consistently associated with HS to date include high weight/obesity, smoking, and female sex. Comorbidities in patients with HS encompass metabolic, endocrine, psychiatric, and inflammatory diseases.

Conclusion: Further research is warranted to enable clinicians with the knowledge necessary to manage patients presenting with HS and to deliver patients the disease-modifying treatment and care that they require. Several practical points may be discerned from research regarding risk factors and diseases associated with HS. These include raising the index of suspicion for certain physical diseases and mental conditions in patients with HS and lowering the biopsy threshold for certain malignancies.

Keywords: Hidradenitis suppurativa, Acne inversa, Systematic review

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease primarily affecting the apocrine gland-rich areas of the body. It presents with painful nodules, abscesses, sinus tracts, and scarring[1]. It is a destructive, deforming disease, and has a significant impact on patient quality of life. The first clinician to describe HS was Velpeau in the year 1839[2]. However, it has only been acknowledged as a separate disease entity in recent years, as previously, it was thought of as a variation of acne vulgaris[3]. Much contemporary research has therefore been conducted on the disorder revealing important insights into its pathogenesis and risk factors. HS is now known to be a unique multifactorial disease whose pathogenesis involves an intricate interplay between genes and environmental factors[2]. This literature review aims to ascertain what research has revealed regarding the pathogenesis of HS, the risk factors, and diseases associated with the disease. In doing so, the authors intend to provide an up-to-date understanding of HS to assist in the clinical diagnosis, screening, and management of patients with this challenging disease.

Table 1. **Oxford Levels of Evidence**

Level	Type of Study
Ia	Systematic Review (SR)/Meta-analysis (MA)
Ib	Individual Randomised Control Trial
IIa	SR/MA of Cohort Studies
IIb	Individual Cohort Study
IIIa	SR/MA of Case Control Studies
IIIb	Individual Case Studies
IV	Case Series
V	Expert Opinion

Methods

Review of Papers Relating to Pathogenesis of HS

Ovid, PubMed, Web of Science, and the Cochrane Library were systematically searched using the keywords: "*hidradenitis suppurativa*" or "*acne inversa*". All papers

that were relevant to the review were included and any duplicates were removed. A total of 40 articles were identified. Only articles with the level of evidence IIIb according to the Oxford Centre of Evidence-Based Medicine **(Table 1)** or superior have been included, any levels of evidence below this were deemed not to have an adequate level of objectivity. As HS was only considered a disease entity in itself in the 1990s, articles from the period of 1990–2018 were selected for inclusion. Other reasons for exclusion were that the text was not available in full, or that it was written in a non-English language.

Of all papers screened using these parameters, 19 were excluded, leaving 21 which were fully assessed for inclusion. 1 paper was subsequently excluded. Thus, 20 studies in total were selected for inclusion in this review **(Figure 1)**.

Review of Papers Relating to Risk Factors of HS

The review of literature pertaining to the risk factors and diseases associated with HS was conducted as above for papers relating to the pathogenesis of HS.

A total of 48 articles were collected. Of all papers screened using the parameters defined above, 10 were excluded. The 38 remaining articles were fully assessed for inclusion, with none of these being subsequently excluded. In total, 38 studies were used for the data in this review **(Figure 2)**.

Results and Discussion

Pathogenesis and Mechanism of HS

Our search results for pathogenesis yielded 20 papers in total: 9 case reports, 6 case-control studies, and 5 cohort studies, as summarised in **Table 2**.

The papers encompassed a wide array of data pertaining to various theories and hypotheses regarding the pathogenesis of HS. Although the pathogenesis of HS is still not well-understood, the data maintains that there appears to be a dysregulation of the adaptive and innate immune systems. For instance, one cohort study identified an upregulation in certain inflammatory cell types in HS including IFN-γ and TNF-β/LT-α[23].

A genetic link conferring a predisposition for the development of HS in certain forms of the disease has also been identified. A case report in 2017 stated that HS can be caused by a mutation in γ secretase which is responsible for the Notch signalling pathway[9]. This theory is also supported by a cohort study from 2012 in which the γ-secretase genes NCSTN, PSENEN, and PSEN1 were shown to contribute to rare forms of HS[21]. The Notch pathway is important for maintaining the inner and outer root sheath of the hair follicles. When there is deficient Notch signalling it results in conversion of hair follicles to keratin-enriched epidermal cysts. This can result in a Toll-Like Receptor (TLR)-mediated innate immunity.

A case report from 2017 defined HS as an inflammatory disorder of the follicular epithelium, however a secondary bacterial infection can often occur[9]. A cohort study published in 2018 suggested that HS is due to an exaggerated inflammatory response which may be driven by dysbiotic commensal bacteria and/or biofilms[20].

While a lot of attention has been given to the cellular and molecular biology of the host tissues affected by HS, less attention has been given to the bacteria involved and the potential involvement of the cutaneous microbiome. A case report conducted in 2012 suggested that HS should be considered as part of bacterial biofilm-based disorders due to the clinical features of HS couple with the supporting bacterial communities[12]. A case-control study published in 2017 investigated whether the cutaneous microbiome of 30

Figure 1. **Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) Chart for Papers Relating to Pathogenesis of HS**

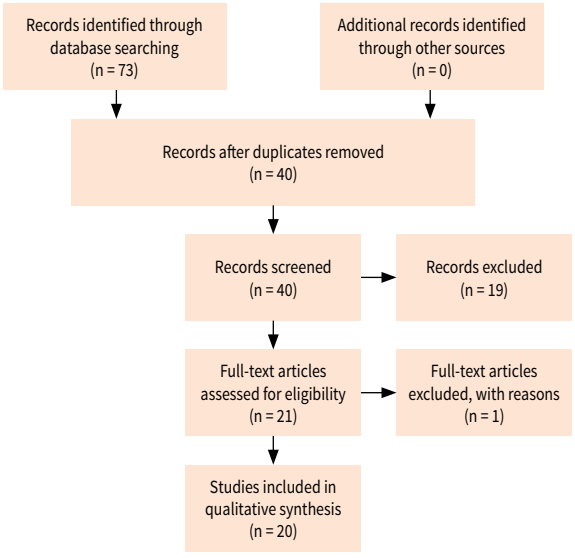
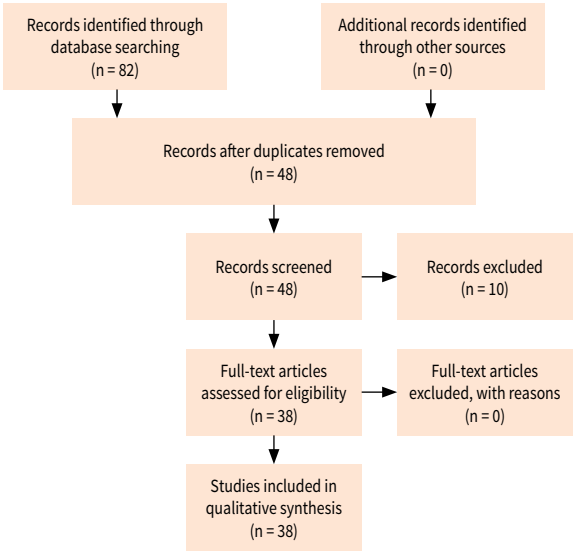


Figure 2. **PRISMA Chart for Papers Relating to Risk Factors of HS**



HS patients differed from that in 24 healthy controls[15]. They identified five microbiome types and their resulting data suggested that a dysbiotic microbiome may have a role in the pathogenesis of HS. The use of next-generation sequencing analysis provided a previously unreported description of the microbiome in HS as previous studies had relied on culture-based methods, which often suggested commensal bacteria[22]. Previous studies have also been restricted to lesional skin while this study included both non-lesional skin of HS patients and healthy controls.

A case-control study conducted in 2017 investigated the global DNA methylation and hydroxymethylation status in lesional and perilesional HS skin compared to healthy controls. To date there have been no previous reports on the imbalance between methylation and demethylation concerning patients with HS. While their results showed no difference in global DNA methylation, they did find an imbalance in DNA hydroxymethylation suggesting that it may play a role in the pathogenesis of HS and hence may pose as a future therapeutic target[13].

Risk Factors and Associated Disease

This section of the review encompassed 38 papers in total: 8 case reports, 11 case-control studies, and 19 cohort studies relating to the risk factors and diseases associated with HS. These are listed in **Table 3**.

Although this provided a wide scope of data pertaining to the factors with HS, it must be noted that some studies did not provide as much detail as to which risk factors and comorbidities were accounted for in their sample as others. Therefore, several associated factors may appear rarer than their actual clinical frequency due to their omission from select studies' interest criteria. Several other associated factors may have seen an antithetical rise in their apparent clinical frequencies due to a trend of inflated interest in those factors at some time. Non-modifiable risk factors that have been consistently identified include female sex and a positive family history. Those factors and co-morbidities, which appear to have the most bearing on clinical practice, will be henceforth discussed. These include weight, inflammatory bowel conditions, cardiovascular disease, psychiatric disorders, and malignancies.

Associated factors pertaining to increased weight, namely obesity, overweight, and high BMI, were among the most commonly observed, collectively appearing in 21 of the papers reviewed. Factors in the arena of smoking were also found to be highly frequent fixtures, with 23 papers marking the activity a significant factor in their investigations. Factors relating to malignancy were also elucidated as significant in a selection of studies. Most notable among these factors were those of squamous cell carcinoma (SCC) (4 studies), hepatic carcinoma (2 studies), and haematological malignancies (2 studies). Associated factors regarding inflammatory bowel disease (IBD) were highlighted in 4 studies, chief among the factors being Crohn's disease, which was discussed in all 4 of the same papers. Furthermore, Egeberg, Jemec, et al. discovered a significantly increased risk of new-onset Crohn's disease and new-onset ulcerative colitis in patients with HS, implying that these IBDs are more likely to be comorbidities of HS than risk factors for the development of HS[49].

A cohort study performed by Egeberg, Gislason, et al. determined there to be a significantly increased risk of cardiovascular-associated death in patients with HS, pointing to increased risks of myocardial infarction and ischaemic stroke as pertinent comorbidities of the disease[55]. Hypertension was found to be another cardiovascular associated factor, with 7 studies reporting its significance, as were subclinical atherosclerosis[36,37], greater carotid intima-media thickness[37], and carotid plaques[37].

Psychiatric disorders were found to be significantly associated factors in 5 papers. Depression was marked as a significant factor in 3 cohort studies, while

Table 2. **Search Results for the Pathogenesis and Mechanism of HS**

Pathogenesis Factors	Number of Papers				Reference(s)
	Total	a) Case Reports	b) Case Control Studies	c) Cohort Studies	
Enhanced expression of tumour necrosis factor (TNF)-α	7	6	0	1	a) 4, 5, 6, 7, 8, 9 c) 20
Enhanced expression of interleukin (IL)-1β	2	1	0	1	a) 4 c) 18
Enhanced expression of IL-17	4	2	0	2	a) 4,5 c) 18, 20
Loss of function of γ-secretase multiprotein complex which regulates the Notch signalling pathway	3	2	0	1	a) 6, 9 c) 21
IL-12/Th1 pathway elevation	1	1	0	0	a) 5
Deficiency of IL-22 and IL-20 in HS lesions	1	1	0	0	a) 5
Abnormal expression of innate immunity markers (toll-like receptors 2, 3, 4, 7, and 9; intercellular adhesion molecule 1; interleukin [IL] 6 and 10; tumour necrosis factor; α-melanocyte stimulating hormone; transforming growth factor β; β-defensin 2)	9	6	1	2	a) 4, 5, 6, 7, 8 b) 17 c) 18, 20
Blockage of IL-2	1	1	0	0	a) 10
Prosthesis-related friction	1	1	0	0	a) 11
Bacteria biofilm	6	2	3	1	a) 7, 12, b) 15, 16, 19 c) 22
Interferon-gamma (IFN-γ) elevated in the HS	1	0	0	1	c) 23
Higher levels of tumour necrosis factor-β (TNF-β)	1	0	0	1	c) 23
Increase in serum C5a	1	0	0	1	c) 20
Reduction of components in the proximal part of the complement pathway (C3, C4, and iC3b)	1	0	0	1	c) 20
Imbalances in DNA hydroxylation	1	0	0	1	b) 13
Role of anti-cytokine autoantibodies (c-aAbs)	1	0	0	1	b) 14

Table 3. **Search Results for Risk Factors and Diseases Associated with HS**

Associated Factor(s)	Number of Papers: Total	a) Case Reports	b) Case Control Studies	c) Cohort Studies	Reference
Obesity/Overweight/High BMI (Body Mass Index)	21	2	10	9	a) 24, 25 b) 22, 32, 34, 35, 36, 37, 38, 39, 40, 42 c) 33, 43, 44, 45, 48, 50, 51, 52, 56
Increased waist circumference	4	0	4	0	b) 32, 33, 36, 39
Smoking	23	4	6	13	a) 22, 24, 25, 28 b) 32, 35, 37, 38, 40, 58 c) 33, 43, 44, 47, 48, 49, 50, 51, 52, 54, 55, 56, 57
High pack year history	4	2	2	0	a) 24, 25 b) 32, 40
Current smoker	5	0	3	2	b) 35, 37, 40 c) 43, 44
Former smoker	4	0	2	2	b) 32, 35 c) 43, 44
Squamous cell carcinoma	4	3	2	1	a) 25, 26, 29 c) 53
Haematological malignancy	2	1	0	1	a) 27 c) 51
Acute leukaemia	1	0	0	1	c) 51
Hepatic carcinoma	2	1	0	1	a) 31 c) 60
Primary liver cancer	1	0	0	1	c) 60
Diffuse malignant peritoneal mesothelioma	1	1	0	0	a) 29
Non-melanoma skin cancer	1	0	0	1	c) 60
Buccal cancer	1	0	0	1	c) 60
Lymphoma	1	0	0	1	c) 51
Inflammatory bowel disease	4	0	1	3	b) 35 c) 49, 56, 57
Crohn's disease	4	0	1	3	b) 35 c) 49, 56, 57
Ileocolonic and/or perianal Crohn's sisease	1	0	1	0	b) 35
New-onset Crohn's disease	1	0	0	1	c) 49
New-onset ulcerative colitis	1	0	0	1	c) 49
Positive family history of HS	5	1	2	2	a) 24 b) 38, 58 c) 33, 44
Hypertension	7	2	1	4	a) 25, 31 b) 36 c) 43, 51, 56, 58
Renal dysfunction	2	1	0	1	a) 30 c) 43
End stage renal disease	1	1	0	0	a) 30
Diabetes mellitus	11	1	1	9	a) 31 b) 36 c) 43, 44, 47, 48, 49, 51, 56, 60
Gout	1	1	0	0	a) 31
Metabolic syndrome	3	0	3	0	b) 32, 34, 36
High triglycerides	3	0	3	0	b) 32, 36, 39
Low high-density lipoprotein cholesterol (HDL-C)	4	0	4	0	b) 32, 36, 38, 39
High very low- density lipoprotein (VLDL-C)	1	0	1	0	b) 32
High serum insulin	2	0	2	0	b) 32, 42
High C-reactive protein (CRP)	3	0	2	1	b) 32, 42 c) 56
High high-sensitivity C-reactive protein (hs-CRP)	3	0	3	0	b) 32, 36, 37
High homocysteine	1	0	1	0	b) 32
High uric acid	1	0	1	0	b) 32
Elevated erythrocyte sedimentation rate	3	0	3	0	b) 32, 36, 37
High homeostatic model of insulin resistance	2	0	2	0	b) 32, 34
Serum visfatin levels	1	0	1	0	b) 32
Increased systolic and diastolic blood pressure	2	0	2	0	b) 34, 39
High serum glucose levels	3	0	3	0	b) 34, 37, 39
High NOD-like receptor levels	1	0	1	0	b) 36
Subclinical atherosclerosis	2	0	2	0	b) 36, 37
Low total cholesterol	1	0	1	0	b) 37
Greater carotid intima-media thickness	1	0	1	0	b) 37
Carotid plaques	1	0	1	0	b) 37
Female sex	15	0	2	13	b) 38, 42 c) 43, 44, 45, 46, 47, 48, 49, 50, 51, 55, 56, 57, 58
Genital HPV (human papillomavirus) infection	1	0	1	0	b) 41
Increase in neutrophilocytes	2	0	1	1	b) 32 c) 56
Increase in lymphocytes	1	0	1	0	b) 42
Increase in leucocytes	2	0	1	1	b) 42 c) 56
Acne	3	0	0	3	c) 44, 45, 58
Black race	2	0	0	2	c) 45, 50
White race	3	0	0	3	c) 48, 50, 54
Alcohol abuse	3	0	0	3	c) 47, 52, 60
Psychiatric disorder	5	1	0	4	a) 31 c) 47, 50, 51, 56
Schizophrenia	1	1	0	0	a) 31
Depression	3	0	0	3	c) 47, 50, 51
Anxiety	1	0	0	1	c) 47
Antidepressant drug use	1	0	0	1	c) 47
Anxiolytic drug use	1	0	0	1	c) 47
Hospitalisation due to anxiety	1	0	0	1	c) 47
Hospitalisation due to depression	1	0	0	1	c) 47
Increased risk of completed suicide	1	0	0	1	c) 47
Drug addiction	1	0	0	1	c) 55
Age in 3rd or 4th decade of life	1	0	0	1	c) 48
Chronic pain	2	0	0	1	c) 50, 59
Iron-deficiency anaemia	1	0	0	1	c) 51
Pilonidal disease	1	0	0	1	c) 51
Liver disease	2	0	0	1	c) 51, 60
Low socioeconomic status	2	0	0	1	c) 52, 55
Increased risk of myocardial infarction	1	0	0	1	c) 55
Increased risk of ischaemic stroke	1	0	0	1	c) 55
Increased risk of cardiovascular-associated death	1	0	0	1	c) 55
Increased risk of major adverse cardiac events	1	0	0	1	c) 55
Increased risk of all-cause mortality	1	0	0	1	c) 55
Increased risk of adverse cardiovascular outcomes	1	0	0	1	c) 55
Psoriasis	1	0	0	1	c) 56
Polycystic ovary syndrome	1	0	0	1	c) 56
Hypothyroidism	1	0	0	1	c) 56
Atopic dermatitis	1	0	0	1	c) 56
Post-colectomy pouchitis	1	0	0	1	c) 57
Impairment of self-perception	1	0	0	1	c) 59
Impairment of daily living activities	1	0	0	1	c) 59
Impairment of mood state	1	0	0	1	c) 59
Physical discomfort	1	0	0	1	c) 59

schizophrenia, anxiety and drug addiction were factors of similar magnitude in one paper each. It is worthy to note that potential HS-associated factors relating to psychiatric disorders are not explored beyond these 5 papers in either a confirmatory or disproving sense among the remainder of the studies compiled here, pointing to a dearth of interest in furthering research that is inclusive of this realm. The importance of scrutinising the psychiatric comorbidities and risk factors of HS is attested to by the recent work of Thorlacius et al., who discovered a significantly increased risk of completed suicide in patients with HS[47]. Thus, probing the depths of HS's psychiatric associations could prove lifesaving or, at the very least, a benefit to the wellbeing and treatment of patients afflicted by the disease.

Conclusion

Summary of Results

In conclusion, the pathogenesis of HS is yet disputed. Evidence thus far supports an inflammatory component with dysregulation of the innate and adaptive immune systems. Research is ongoing however and with the emergence of modern, more promising research methods, a more concrete characterisation of the pathogenesis of HS is likely to emerge. This in turn will help in the quest to identify and develop better treatment options for afflicted patients.

The risk factors that have been most consistently associated with HS in the research to date include high weight/obesity, smoking, and female sex. Comorbidities in patients with HS encompass metabolic, endocrine, psychiatric, and inflammatory diseases. Though research indicates that the diseases/factors discussed earlier in this review are associated with HS, no common pathogenetic background has yet been determined. Moreover, whether these associated diseases and risk factors are a cause of—or are more often caused by—HS is yet to be conclusively discerned.

Relevance to Clinical Practice

Many questions remain unanswered in the search to identify the pathogenesis and mechanism of HS and provide an understanding of its link to specific risk factors and diseases. Further research is thus warranted to provide clinicians with the knowledge necessary to manage patients presenting with this debilitating disease and to the disease-modifying treatment and care they require.

With regards to empirical work conducted on the risk factors and diseases associated with HS, several points for the practicing clinician may be extracted. Clinicians should consider that HS patients may have ≥1 undiagnosed components of metabolic, endocrine, psychiatric or inflammatory disorders, despite their youth, and initiate appropriate targeted screening. The association between depression, mood disorders and HS should be acknowledged in clinical practice and sought for in the patient presenting with a HS picture. Finally, clinicians should raise their index of suspicion for SCC malignancy and lower their biopsy threshold in HS patients to prevent or minimise SCC metastasis. ◄

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Declarations

The authors declare no conflicts of interest.

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