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COST OF ILLNESS ANALYSIS: HIDRADENITIS SUPPURATIVA

by

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APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated ..01.11.2018..... and numbered ...2018/01-12

Prof. Dr. Bayram YILMAZ
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DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material and study previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

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ABSTRACT

Introduction: Hidradenitis Suppurativa (HS) is defined as chronic, inflammatory, recurring, debilitating skin disease of the hair follicles 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 and also known as Acne Inversa. Due to the few studies regarding economic burden of HS on patients were conducted up to now in US, Europe and Israel, it is inevitable to prepare such a project in the context of HS disease for Turkey. To the best of our knowledge, there has not been any HS cost of illness (CoI) study conducted in Turkey. Therefore, the aim of this study is to estimate the yearly cost of HS disease in Turkey with the perspective of the Turkish Ministry of Health.

Material and Methods: This is a prevalence-based CoI study in focus on direct health care costs with the perspective of Ministry of Health which means the payer. A multipoint data collection procedure has been done based on the literature search regarding HS epidemiological data, treatment choices and direct health care costs in order to obtain the necessary data for the analysis and the structure of CoI of HS. A literature search on studies published in English on HS was performed in PubMed with the key words of "Hidradenitis Suppurativa", "Acne Inversa" and "Verneuil Disease" from 1949 to November 2017. Disease itself and treatment options have been reviewed comprehensively.

Results: Total numbers of Turkish people with HS has been estimated as 79.815 according to 0.10 % prevalence rate of Garg and his colleagues' prevalence study. The 12 months cost were estimated as 20.807.609,17 TRY (+/- 1.040.380,46 TRY)for patients on Hurley stage I, 622.988.590,40 TRY (+/- 31.149.429,52 TRY) for Hurley stage II and 88.681.664,65 TRY (+/- 4.434.083,23 TRY) for Hurley stage III for the year 2017. We estimated the total direct cost attributable to HS as 732.477.864,22 TRY (+/-36.623.893,21 TRY) and revealed that average one-year direct cost per patient was

9.177 TRY (+/- 458 TRY) which can translated as 192.757.332,69 USD (+/- 9.637.866,63 USD) and 2.415 USD (+/- 120 USD) respectively..

Discussion and Conclusions: Medications seem to be only the definitive important resources funded by the Turkish public health system. Even though the studies' methods are different, it is possible to compare the results of other available HS CoI studies with our study. Cost per patient seems similar between the studies but source and the proportions of the costs were different. Even though HS is a disease which attributed as 'rare' and 'unknown', it is surprising that it takes an important place in terms of treatment costs.

ABSTRACT (Turkish)

Giriş: Aynı zamanda Acne Inversa olarak da bilinen Hidradenitis Suppurativa (HS), genellikle ergenlikten sonra ağrılı, derin yerleşimli, iltihaplı lezyonlar şeklinde görülmeye başlayan; vücudun apokrin bezi taşıyan çoğunlukla aksilla, inguinal bölge ve anogenital bölgelerini tutan; kıl köklerinin kronik, inflamatuvar, reküren ve güçten düşürücü bir cilt hastalığı olarak tanımlanır. Amerika Birleşik Devletleri, Avrupa ve İsrail'de bugüne kadar HS'nin ekonomik yükü ile ilgili az sayıda çalışma yapıldığından, Türkiye için de HS hastalığının ekonomik yükünün belirlenmesi gibi bir proje hazırlamak kaçınılmazdı. Bildiğimiz kadarıyla, Türkiye'de yürütülen herhangi bir HS hastalık maliyeti çalışması yapılmamıştır. Bu nedenle, bu çalışmanın amacı, HS hastalığının yıllık maliyetini Türkiye Sağlık Bakanlığı bakış açısından tahmin etmektir.

Materyal ve Metot: Bu çalışma, ödeyici kurum anlamına gelen Sağlık Bakanlığı perspektifinden, doğrudan sağlık hizmeti maliyetlerine odaklanan prevalans temelli bir hastalık maliyeti çalışmasıdır. HS'nin epidemiyolojik verileri, tedavi seçenekleri ve doğrudan sağlık hizmeti maliyetleri ile ilgili literatür araştırmasına dayanılarak HS'nin hastalık maliyeti analizi ve yapısı için gerekli verileri elde etmek üzere çok noktalı bir veri toplama prosedürü uygulanmıştır. PubMed'de “Hidradenitis Suppurativa”, “Acne Inversa” ve “Vernauil Disease” anahtar kelimeleri üzerinden 1949 ile Kasım 2017 tarihleri arasındaki yayınları kapsayan, HS ile ilgili İngilizce yayınlanan çalışmalar üzerinde yapılan bir literatür taraması gerçekleştirilmiştir. Hastalığın kendisi ve tedavi seçenekleri kapsamlı bir şekilde gözden geçirilmiştir.

Bulgular: Garg ve meslektaşlarının prevelans çalışması baz alınarak % 0.10 prevalans oranına göre HS'li toplam insan sayısı 79.815 olarak tahmin edilmiştir. 2017 yılında Hurley Evre I'deki hastalar için 12 aylık maliyet 20.807.609,17 TL (+/- 1.040.380,46 TL), Hurley Evre II için 622.988.590,40 TL (+/- 31.149.429,52 TL) ve Hurley Evre III için 88.681.664,65 TL (+/- 4.434.083,23 TL) olarak tahmin edilmiştir. Doğrudan HS'ye atfedilebilir toplam maliyet 732.477.864,22 TL (+/-36.623.893,21 TRY) ve hasta başına ortalama yıllık direkt maliyet 9.177 TL (+/- 458 TL) olarak belirlenmiş ve bunun da

sırasıyla 192.757.332,69 USD (+/- 9.637.866,63 USD) ve 2.415 USD (+/- 120 USD) olarak çevirilebileceği ortaya konulmuştur.

Tartışma ve Sonuç: İlaçlar, Türk kamu sağlığı sistemi tarafından finanse edilen en önemli kaynaklar gibi görünmektedir. Çalışmaların yöntemleri farklı olmasına rağmen, mevcut diğer HS hastalık maliyeti çalışmalarının sonuçlarını çalışmamızla karşılaştırmak mümkündür. Hasta başına maliyet, çalışmalar arasında benzer görünmektedir; ancak kaynak ve maliyetlerin oranları farklılaşmaktadır. HS, 'bilinmeyen' ve 'nadir' olarak atfedilen bir hastalık olmasına rağmen, tedavi maliyeti anlamında önemli bir yer tutması şaşırtıcıdır.

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LIST OF SYMBOLS AND ABBREVIATIONS

AI: Acne Inversa

ADA: Adalimumab

AN: Sum of abscesses and inflammatory nodules

a-TNF: Anti-Tumor Necrosis Factor

b.i.d.: Two times a day

BSA: Body Surface Area

CV: Cardiovascular

CoI: Cost of Illness

CD: Crohn's Disease

HiSCR: Hidradenitis Suppurativa Clinical Response

HS: Hidradenitis Suppurativa

HS-PGA: Hidradenitis Suppurativa Physicians' Global Assessment

HSSI: Hidradenitis Suppurativa Severity Index

IBD: Inflammatory Bowel Diseases

IFX: Infliximab

MetS: Metabolic Syndrome

MoH: Ministry of Health

NA: Not Applicable

OR: Odds Ratio

PRO: Patient Reported Outcomes

PsO: Psoriasis

RCT: Randomized Controlled Trial

SpA: Spondylarthritis

UC: Ulcerative Colitis

QoL: Quality of Life

1. INTRODUCTION AND PURPOSE

Hidradenitis Suppurativa (HS) is defined as chronic, inflammatory, recurring, debilitating skin disease of the hair follicles 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 and also known as Acne Inversa (Dessau definition, 1st International Conference on Hidradenitis Suppurativa/Acne Inversa, March 30–April 1, 2006, Dessau, Germany). [1]

Patients suffering from HS due to its enormous burden on patients, and it is highly correlated with concomitant diseases including but not limited to: reduced quality of life, depression, stigmatization, decrease in physical activity, sexual deficiency, and several risk factors associated with cardiovascular diseases. [2]

Over the last years, HS became the one of the hot topic research area and intense researches are conducted in order to develop therapeutical strategies. [3] PubMed searches for 'Hidradenitis Suppurativa' are listed on Figure 1 which is dramatically increasing over the years. Although it was reported to be a rare disease, there are inconsistent prevalence data. Reported prevalence is changing from 0.053% to 4.1% depending to the methodology of the study. [4-11] Moreover, wrong diagnosis regarding identification of HS was started to decline over the last decade. Therefore, revealing pharmacological characteristics and how HS burden on patients affect people and governments became a major problem to be solved. [12]

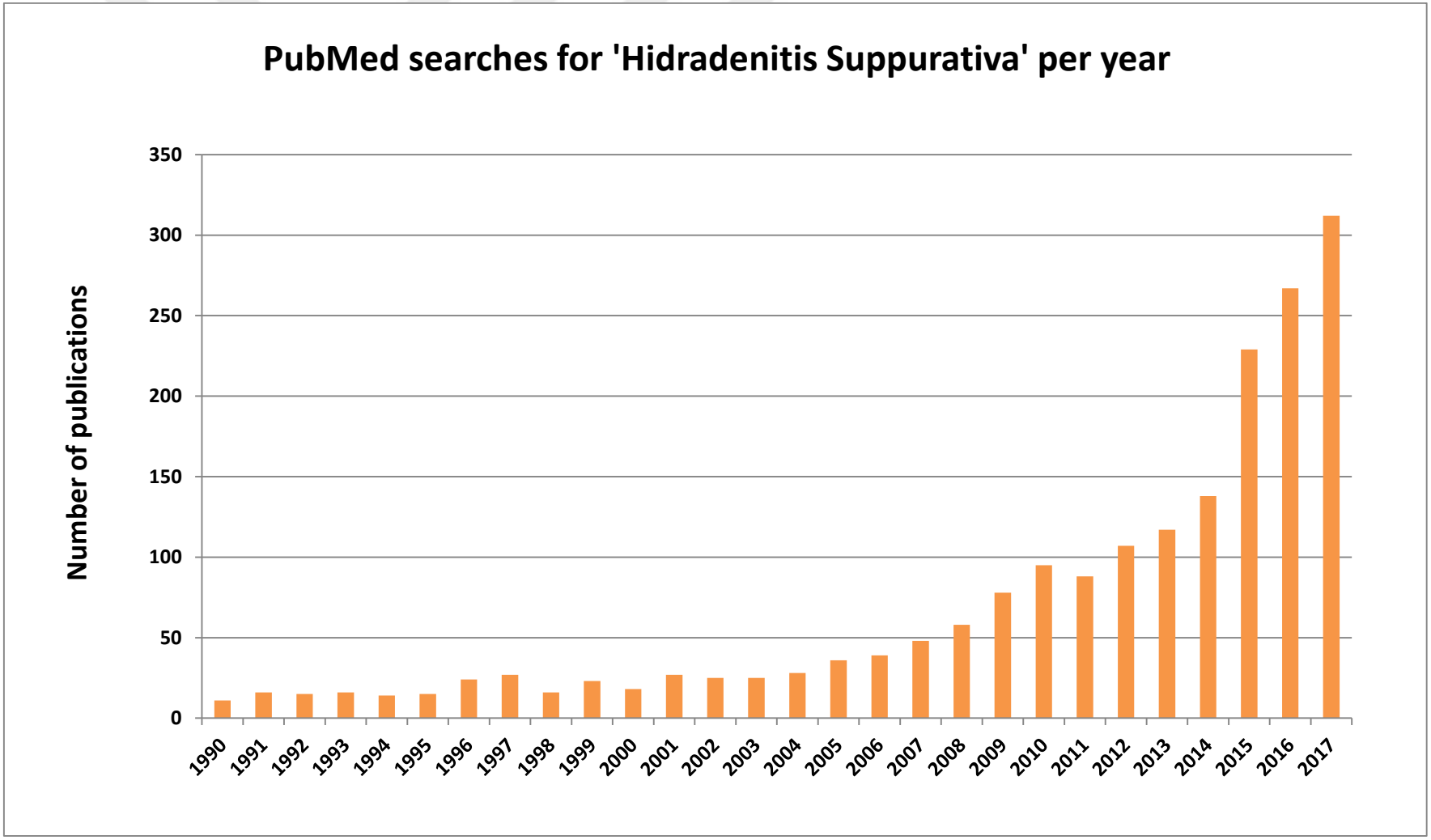


Figure 1 Number of publications regarding Hidradenitis Suppurativa per year

A cost of illness (CoI) study usually translates all of the burden of resource use which are measured as treatment, hospital days, doctor's office visits etc. into monetary terms by putting a unit cost to each element of the burden. Costs as elsewhere in health economics could be direct, indirect (e.g. loss of earnings) and intangible (e.g. pain and suffering). Intangible costs do not usually measure in CoI studies. [13,14] In this study, indirect costs does not taking into account in the analyses due to the lack of adequate data. CoI studies could be done with different perspectives such as societal or government health services.

Due to the few studies regarding economic burden of HS on patients were conducted up to now in US, some of the countries of Europe and Israel [15-22], it is inevitable to prepare such a project in the context of HS disease for Turkey. To the best of our knowledge, there has not been any HS CoI study conducted in Turkey or about Turkey to this study. Therefore, the aim of this study is to estimate the yearly cost of HS disease in Turkey with the perspective of the Turkish Ministry of Health.

In this study, disease itself was investigated in detail and current applicable therapeutical approaches were reviewed in the light of available treatment guidelines. Since there is no available prevalence or incidence data in Turkey about patients with HS, prevalence studies have been searched worldwide. Depending on studies conducted in Europe and USA, prevalence data for Turkey was estimated and number of patients with HS was revealed for Turkey on the year of 2017. Annual burden of HS disease on Turkey was defined as direct medical cost (medical therapies and surgical approaches) with cost perspective of Turkish Ministry of Health accordingly for the year of 2017.

2. LITERATURE REVIEW

2.1. Clinical Aspect of HS

HS defined as inflammatory and recurrent disease, and tender subcutaneous nodules are accepted to be major indicator of HS. Upon appearance of these lesions, they may also give rise to deep dermal and tenuous painful abscesses. [23] Abscesses defined as possessing diffuse and rounded without central necrosis or pointing and exuding with a suppurating drainage. [24] Although inflammatory abscesses heal at the end, they often resulted with scarring, fibrosis and rigidity of the skin. The disease is latent, and tends to be occur in developing healthy post pubertal females and males. [25]

In inverse apocrine gland areas of the armpit, perianal, inguinal, perineal, buttock, mammary, inframammary, groin, chest, scalp, HS lesions more likely to be appear. [23] Burning, pruritus, heath in the lesions, excessive sweating, and pain are described as initial symptoms and signs of HS. [26]

2.2. Pathology of HS

From first description of the disease to the present date, pathogenesis of HS has been described in different aspects and the exact pathogenesis of HS is still not clear and unproven. [27]

French physician, Velpeau, firstly described HS in 1839. [28] Velpeau and his colleagues reported a novel case study which described inflammation with skin-deep abscesses affecting the axilla, mammary and perianal areas were observed. [28] In 1854, Ramasastry and colleagues reported successive patients with similar lesions in groin and armpits, then he suggested was suppurating inflammation of the sweat glands could major responsible factor for HS. [29] The theory was accepted for more than a century.

Successive reports indicated that HS pathogenesis is more complex than it was thought, and suggested to be apocrine glands associated disease in those years. However, it has been resulted that HS is a disorder of follicular occlusion rather than apocrine glands. [30] Although it was not clearly understood whether it causes because of immune dysregulation firstly appear and followed by follicular occlusion, but it is clear that both play a crucial role. [31]

Regulation of both innate and adaptive immune dysregulation were reported to be due to decrease in expression of antimicrobial peptides, followed by excessive

inflammatory response with the overexpression of pro-inflammatory cytokines such as some of the interleukins (IL) and tumor necrosis factor-alpha (TNF-a) in HS lesions. [32] Not only factors indicated above conduce to HS, but also bacterial activity, over-sweating, abnormous infolding of the epidermis resulted with scarring and deficiency in sebaceous glands numbers. [31]

As a result, it has been accepted that, occlusion and following inflammation of the hair follicle is triggered by both genetic and environmental factors which is shown on figure 2. [27]

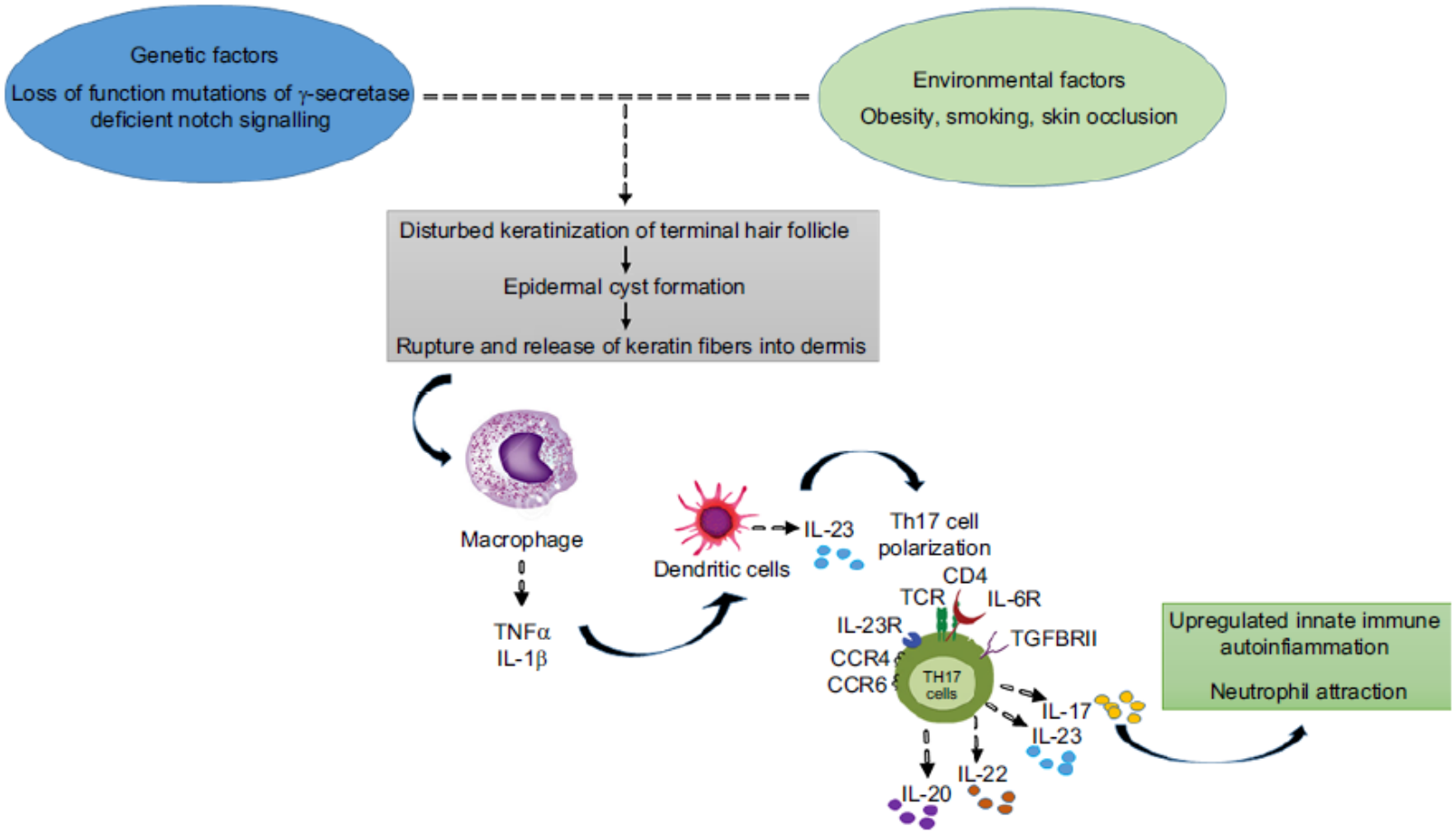


Figure 2. Pathophysiology of HS

2.3. Risk Factors of HS

In successive studies, several associations between HS and genetic background of family, endocrinologic factors, obesity, smoking and other factors were reported.

2.3.1 Genetic Factors

Study of Fitzsimmons and Guilbert depending on analysis of 26 subjects with HS and their families' samples derived for a three year period. Moreover, family pedigree and other family related background information combined in analysis and results revealed that approximately one third of the first-degree relatives of patients had HS also. [33] Both of males and females were affected via vertical transmission through several generations. Many of the first-degree relative participants were under the second decade of their life during the study. Depending on results, it was suggested that if the time of subjects analysis was performed in longer time interval, much more of them would progress the disease and would increase the percentage of affected subjects closer to 50%. [33] In the light of this prediction, Von der Worth et al revised analysis of these families after 15 years and revealed that observed the additional cases of HS. [34] However, he reported that transmission rate was still lower than 50% associated with inheritance. Afterwards, they thought that this might be due to their strict disease definition, partial penetrance, and hormonal effects. [34]

2.3.2 Endocrinologic Factors

Over the years, many studies reported conflicting findings about the role of hormones in HS.

Mortimer and his colleagues, for instance, found that female patients with HS could develop depending androgenic manner. In the study of Mortimer's, female patients with HS were reported to have higher aperiodic menstruations, premenstrual exacerbations of HS, hirsutism and acne vulgaris. Moreover, female patients had higher amount of testosterone level compare to control group. [35]

In another study, Barth and Kealey examined histologically isolated axillary glands obtained from five female patients with HS and age-matched controls. Depending on measurement of enzyme activity trough use of appropriate substrates, they reported that androgen levels in the group of patients with HS were either reduced or weren't significantly contrasting compared to patients without HS. In the light of

these findings, they proposed another hypothesis arguing to a basis for hyperandrogenism in female HS patients. [36]

On the other hand, Barth et al suggested that higher level of free androgen index contributes less to the HS pathogenesis. In addition, women HS patients compared to weight matched patients without HS and both groups were also matched for hirsutism. However, no differentiation was detected in testosterone level of the plasma and levels of dehydroepiandrosterone hormone. [37]

Karagiannidis and his colleagues highlighted on their review study that for sure, endocrinological factors play some role in disease pathogenesis and maintenance but exact association between hormones and occurrence of HS still remains unclear. Additionally, they suggested that hormonal therapies such as antiandrogens and metformin might be a therapeutic option for recalcitrant HS cases. [38]

2.3.3 Obesity

It has been suggested that there is a correlation between obesity and HS. In a study conducted by Rompel and Petres with 106 patients, it has been observed that the 51.6% of the patients with HS were obese, with 21.5% were morbidly obese. [39] In a study Harrison et al demonstrated that the percentage of overweight male patients with HS was 77% and the percentage of obesity was 26% while the percentage overweight female patients was 69% and the obesity ratio of was 33%. A significant correlation between body mass index and HS was reported. [40]

Obesity may provoke the disease using different mechanism of action such as; via sweat expression and susurration, hormonal metabolism dysfunction and shearing of follicular/ductal outlets. [41,42] These results are aliasing with the enfolding of skin and following friction, susurration, and blockade of the skin. Moreover, depending on shearing effect, subsequent increase in skin friction may induce follicular hyperkeratosis and occlusion trough mechanism of epidermal shedding. [43]

In a recent study, depending on investigation of HS patients having higher prevalence of metabolic syndrome with obesity reported dysfunctional regulation of metabolism could be a major contributive element in HS progression, specifically for young patients. [44]

2.3.4 Smoking

Cigarette smoking is a significant risk factor for both the development of HS and severe disease. Body-mass index and tobacco smoking have been directly correlated with the severity of this condition. [45]

Studies demonstrate increasing prevalence of smoking among HS patients. Study of Revuz et al shows the correlation of smoking in patients with HS. Regardless, this connection has not been showed for patients who used to smoke. [5]

It has been proposed that smoking may induce altered chemotaxis by altering neutrophilic granulocytes, can change the activity of sweat glands, can emit toxic metabolites in the sweat gland activity and toxic metabolites in sweat. Accordingly, it is believed that the disease or increase the disease activity. [23]

In the matched case-control study of König and his colleagues, the contingents of having HS disease were 9.4 times bigger than people who don't smoke or ex-smokers. [46] In another study it has been demonstrated that the smoking is correlated also with the sereneness of HS. Smoker patients had considerably higher sereneness scores than non-smoking patients, and formerly smoking HS patients had mid-level scores. [47] On the other hand, another study involving 302 patients show that the single variable analysis of data obtained from this study from a single center not succeed to show an relationship with cigarette smoking and HS sereneness. [48] But it is still unclear that whether cessation of smoking affects the disease progression of HS or not. [44]

2.3.5 Bacterial Factors

Bacterial infection was accepted to be an important regulator of HS pathogenesis. Although different reports on HS bacterial activity have revealed contradictory results, the major difference could be due to the different methods utilized to get the bacteria. At previous studies, bacteria were obtained from the faced of HS lesions and samples were inclined to taint with the flora of the skin. Several types of bacteria have been identified in cultures collected from the faces of HS lesions, including but not limited to: Staphylococcus milleri, Staphylococcus aureus, Streptococcus viridians, anaerobes, coryneform bacteria, and Gram-negative rods. [49]

It has been widely accepted that bacteria in the lesions of HS are more likely play a secondary role in HS, instead a primary. [50]

2.3.6 Other Factors

Woman gender is also accepted as a risk factor for HS. According to current literature, it has been suggested that women are more often affected than men. [1] Revuz and his colleagues showed that female: men ratio is about 3:1. [5]

In a retrospective based approach study, 10 out of 45 patients showed the story of mechanical irritation before beginning of the disease. Indicated originations of the trauma were divers, and differentially appeared. [51] In another study by Mustafa et al, it was resulted that use of antiperspirants increased progress of HS. In different studies, the mechanism of action of antiperspirants was explained. For example, they indicated that antiperspirants could cause HS flares trough shaping of an occlusive film over the armpits.[52] Moreover, antiperspirants were suggested to be trigger in HS trough chemical aggravation which causes poral blockage or modifying the flora of the axillary area.

In addition, the mechanism of obesity correlated with retaining sweat, so exacerbating the role of antiperspirants as a counterirritant in HS. [53]

Several reports on beginning of HS or flare after start of lithium treatment indicate that HS might be the potential fallout of lithium. It has been discussed that the underlying root is lithium's capability to elevate neutrophil migration and phagocytic ability as well as to increment epithelial cell proliferation, or lithium's capability to cause follicular blocking via its straight effect on follicular keratinocytes. [54]

2.4. Diagnosis

Patients with HS dealing with serious misdiagnosis issue because of the low disease awareness among health care professionals and also in patients. Saunte and colleagues showed on their study that diagnostic delay for HS patients is 7.2 years from the onset of the first symptoms. [55]

In the clinical diagnosis of HS, there is no room for biopsies which are not routinely used and there are no validator laboratory assessments for HS. Despite the criterial of diagnosing HS may change, typically diagnosis include the factors of; recurrence of lesions, chronicity, lack of clearance from antibiotics, sinus appearance and scarring, dermal contracture, multifocal lesion distribution, existence of variety of comedones, nodules, papules, soreness of lesions and suppuration. [26]

Primary diagnostic criteria of HS depend on history of the patients and clinical presentation of the disease. Symptoms include but not limited to; involvement of axilla,

genitofemoral area, perineum, gluteal area and infra-mammary area of women, appearance of nodules (inflamed or non-inflamed), sinus tracts (inflamed or non-inflamed), abscesses and scar formation (atrophic, mesh-like, red, hypertrophic or linear). [56]

Three criteria should be met for the diagnosis;

- Typical lesions; which is deep-seated painful nodules
- Typical lesions; that the disease must occur in 1 or more of the typical areas: axillae, inframammary and intermammary folds, groin, perineal region, or buttocks.
- Chronicity and recurrence [57]

2.5. Associated Diseases

HS has been linked to several different adjuvant and secondary diseases, include obesity, metabolic problems, inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, spondyloarthropathy, follicular occlusion syndrome and other hyperergic disease. [58]

Among these diseases, IBD, especially Crohn's disease (CD), is the most reported associated disease in patients with HS. Principi and his colleagues showed on their recent pooled data analyses study that prevalence of HS in IBD patients was 12.8%. 17.3% of the patients with CD and 8.5% of the patients with ulcerative colitis (UC) had HS as comorbid disease. [59]

Spondylarthritis (SpA) is also linked to HS as a frequent comorbid disease. Schneider-Burrus et al showed that back pain and SpA are very common among patients with moderate/severe HS. As result, more than 70% of HS patients were suffering from back pain. [60]

The other signification type of disorders correlated with HS are follicular occlusions which is described as dissecting cellulitis of the scalp, acne conglobata and pilonidal cyst are reported as a comorbidity to HS and contribute formation of "follicular occlusion tetrad". Previous appearance of significant acne in family history (long lasting, leaving scars) is collected of males and females, in 44% and 23%, respectively. [48]

2.6. Prevalence of Hidradenitis Suppurativa

Prevalence of HS was reported with different rates over the year. HS prevalence is a topic of discussion; witch relevant data starts from 0.053% to 4.1% of the population. It should be noted that there are many differences available in the research methodologies and populations that studied in. [4-11] Summary of prevalence studies have been sown on Table 1.

Jemec conducted a study among women on 1988 for to establish the role of androgens in HS and prevalence data also revealed. 70 female patients included to the study. Prevalence was found to be 4%. [8]

On 1996, Jemec and his colleagues conducted another study for to describe the 1-year point prevalence of HS and its potential precursor lesion. They pick 599 persons as an unselected sample from the general population and 507 persons who undergoing screening for sexually transmitted diseases. Point prevalence was found as 4.1% and 1-year prevalence of HS was determined as 1%. [6]

Revuz and his colleagues conducted a study on 2008 in a representative sample of the French population (n = 10,000). An online survey was used for to evaluate the major dermatological disorders in the French population and any associated factors. Results showed a prevalence of 1%. [5]

Cosmatos et al conducted a study in United States by using a large health care claim database with the objective to estimate the prevalence of HS on 2008. They included 7927 patients to the study. They found a low rate of clinically detected HS which prevalence was 0.053%. Results showed that affected person almost 3 times as likely to be woman and the highest prevalence was on 18 to 44 years of ages. [7]

As a supportive data to Cosmatos', Sung and Kimball conducted a similar study. They assess the prevalence of patient with HS seen at Massachusetts General Hospital in the years 2007 and 2011 to determine if prevalence rates were similar. They found 494 HS patients out of 429,329 patients. Prevalence of HS calculated as 0.11%. [10]

Vinding et al showed in a population sample of over 16,000 persons that self-reported symptoms compatible with the diagnosis of HS occurred in 2.1% on 2013. Results suggest that women are more likely to be affected. [9]

Shahi and his colleagues conducted a population based study on 2014 at Olmsted Country, Minnesota. They used the data from Rochester Epidemiology Project which is a unique infrastructure that combines and makes accessible all medical records

in Olmsted County since the 1960s. Results revealed a total one-year prevalence of 127.8/100,000 which can be translated as 0.13%. [4] As a supplementary data, overall one-year incidence was found as 6/100,000 on the same project. All the data analyzed as sex and age adjusted. The data also supports the idea that HS is a rare diagnosis. [61] It has been shown that the incidence level increases importantly in female who 18 to 44 years of age. Despite it can be said that HS may be seen greatly in certain races, it is however still not clear. [62]

And a very recent study has conducted by Garg and his colleagues on 2016. They analyzed 48 million unique patients across all United States regions by using electronic health record data. Results showed 47,690 HS patients and overall HS prevalence in United States was 0.10%. [11]

Table 1 Summary of HS Prevalence Studies

Country	Number of sample	Population	Prevalence Estimation	Reference
Denmark	70	Female patients	4%	Jemec, 1988 [8]
Denmark	599	Adults	4.1%	Jemec, 1996 [6]
France	10,000	Adults	1%	Revuz, 2008 [5]
United States	7,927	Patients	0.053%	Cosmatos, 2008 [7]
United States	429,329	Patients	0.11%	Sung, 2011 [10]
Denmark	16,404	Adults	2.1%	Vinding, 2013 [9]
United States	144,000	People	0.13%	Shahi, 2014 [4]
United States	48 Million	Patients	0.10%	Garg, 2016 [11]

2.7. Impact on Quality of Life

Negative aspect of HS on quality of life (QoL) was suggested to be greater than other dermatological factors. The negative impact of HS QoL is considerably important and it could interrupt the everyday activities of individuals including but not limited to walking or social embarrassment since purulent discharge or odor of the abscesses. [63]

These factors together with smell, exudate, pain, and the need for frequent dressing changes could lead major negative effects on patients' daily activities. [64]

HS is also related with a number of comorbidities and disorders, including metabolic syndrome, other autoimmune diseases (Crohn's disease, axial spondylarthrosis etc.) and mostly obesity which have a great effect on patients' QoL. Hence, majority of the patients with HS have to handle depression, stigmatization and embarrassment. Adding to that, fever and fatigue frequently develop along with the lesions in severe cases. As result, patients may not be able to perform even routine daily works. [56]

2.8. Classification and Staging

Many different models have been developed to classify and stage HS and to assess the treatment success, such as qualitative models as Hurley Staging System and Refined Hurley Staging System. And there are also quantitative models, such as the Sartorius and the modified Sartorius systems, the Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA), and the Hidradenitis Suppurativa Clinical Response (HiSCR). [2] Among these classification and staging tools, the most widely used scale for to assess disease severity is the Hurley Staging system and HS-PGA. [2]

2.8.1 Hurley Staging

Hurley reported the Hurley Staging System, as a novel classification model to define HS in 1989. It is sufficient to classify between 3 different levels of disease severity (Table 2). [65] Hurley staging is proposed as a tool to facilitate rational treatment decision-making for surgical approach in a certain body location. [65]

Hurley staging model was extensively used due to its suppleness and rapidness. But it also has some limits, such as insufficient qualitative and its unvarying nature. If we put it differently, neither count of affected anatomical locations nor the count of lesions at each location was described by this model. Besides, it also considers scars and fistulas as certain fixed or invariable characteristics which are not very effective for assessing response of the therapy. [2]

Table 2. The Definition of Hurley Staging

Hurley Stage	Definition
I	Individual primary lesions and/or cysts without fistulae or scarring
II	Individual primary lesions and/or cysts with presence of fistulae and scarring
III	Confluent primary and secondary lesions at involved surface(s) with fistulae and scars

A recent study group consist of Dutch experts has been suggested to Refined Hurley Staging System. Expert Group's classification and below treatment ladder system (Figure 3) provide an easy way for a holistic therapeutic plan with inclusion of body surface area (BSA). Team suggests that the modifications of the Hurley system help the clinician to guide therapy, especially in the choice between surgery and/or adjuvant anti-inflammatory drugs. [66]

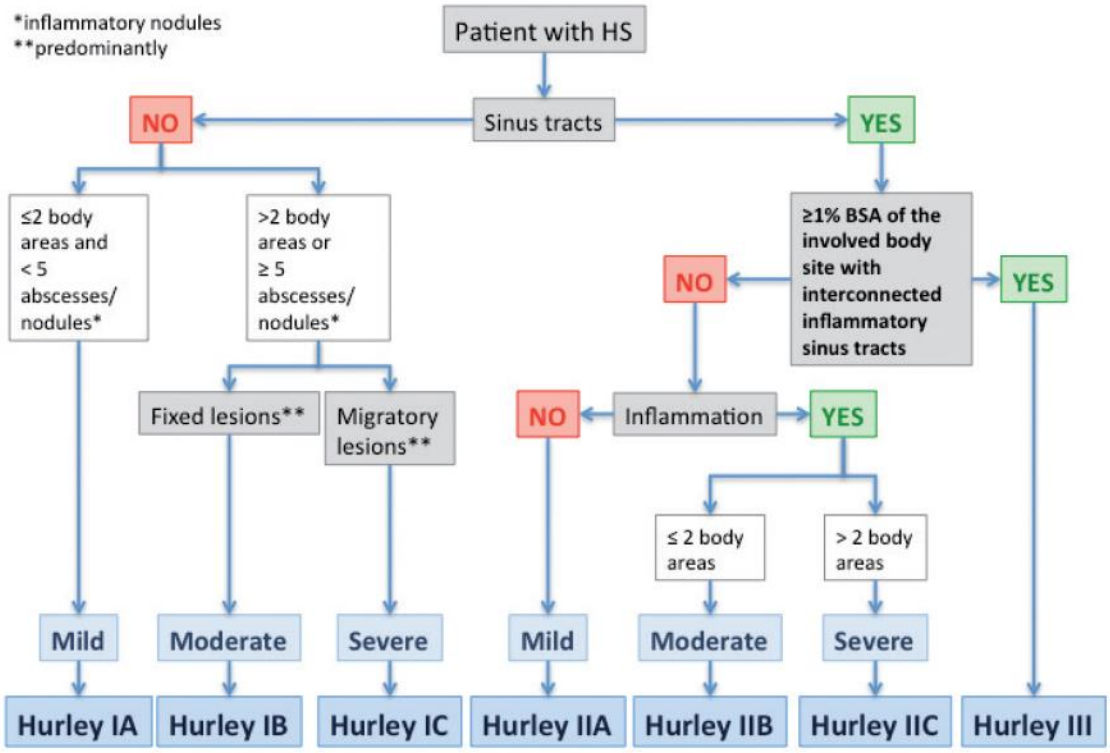


Figure 3. Refinement of the Hurley Classification

2.8.2 Hidradenitis Suppurativa - Physician's Global Assessment

The HS-PGA is one of the most largely used classification assessment models for to assess the response to medical treatment in both clinical research and clinical practice. [2] HS-PGA classifies disease severity into 6 categories as clear, minimal, mild, moderate, severe and very severe based on the number of abscesses, fistulas, inflammatory nodules, and non-inflammatory nodules in all anatomic areas which is shown on Table 3. [67]

Table 3. Hidradenitis Suppurativa - Physician's Global Assessment

Stage	Score	Definition
Clear	0	No abscesses, no draining fistulae, no inflammatory nodules and no non-inflammatory nodules
Minimal	1	No abscesses, no draining fistulae, no inflammatory nodules but presence of non-inflammatory nodules
Mild	2	No abscesses, no draining fistulae and 1 – 4 inflammatory nodules, or 1 abscess or draining fistula and no inflammatory nodules
Moderate	3	No abscesses, no draining fistulae and ≥ 5 inflammatory nodules, or 1 abscess or draining fistula and ≥ 1 inflammatory nodule, or 2 – 5 abscesses or draining fistulae and <10 inflammatory nodules
Severe	4	2 – 5 abscesses or draining fistulae and ≥10 inflammatory nodules
Very Severe	5	>5 abscesses or draining fistulae

2.8.3 Sartorius Score

Disease severity on HS can be assessed either with the Hurley staging system or the Sartorius scoring system. The Hurley staging system is more clinically appropriate

while the Sartorius system is used principally for clinical trials. The Sartorius Scoring system is consisting of number of affected body parts, sinus tracts and nodules with determined points as below (Table 4). [30]

Table 4. The Definition of Sartorius Scoring System

Categories	**Points per Parameter**
Anatomic region involved	Axilla - 3 points Groin - 3 points Genital - 3 points Gluteal - 3 points Inframammary - 3 points Other inflammatory region- 3 points
Number and score of lesions	Each nodule - 2 points Each fistula - 4 points Each scar - 1 point Each "other" - 1 point
Longest distance between 2 relevant lesions	Less than 5 cm - 2 points Less than 10 cm - 4 points More than 10 cm - 8 points
Lesions clearly separated by normal skin in each region	Yes - 0 point No - 6 points

2.8.4 Modified Sartorius Score

Sartorius system was subsequently modified by Sartorius and then Revuz for a more practical approach. [68] Similar to actual Sartorius Scoring System, the modified system also assess the number of the body areas involved, the number and type of

lesions in each anatomical location, the length between two most related lesions, and the presence of normal skin separating these lesions. Addition to that, Modified Sartorius Score takes into account the count of inflammatory lesions for example nodules and fistulas in armpits, groin, and buttocks. The system calculates a total score which is shown at Table 5. [68]

Table 5. The Definition of Modified Sartorius Scoring System

Categories	**Points per Parameter**
Number of areas affected	Per area – 3 points
Number and severity of lesions	Nodules – 1 point Fistulas – 6 point
Longest distance between 2 relevant lesions (or size if there is a single lesion)	<5 cm – 1 point 5-10 cm – 3 points >10 cm – 9 points
All lesions are clearly separated by normal skin	Yes – 0 point No (Hurley III) – 9 points

2.8.5 Hidradenitis Suppurativa Clinical Response

HS Clinical Response was recently developed and validated for the assessment of anti-inflammatory treatment effectiveness, to measure the disease sereneness and to create a significant clinical end point. It requires counting inflammatory nodules, abscesses and draining fistulae at baseline and after the intervention. [69]

The HiSCR is a measure for assessing response to medical treatment; it is not considered a classification model. The HiSCR is defined as a reduction of 50% of more in inflammatory lesion count as sum of abscesses and inflammatory nodules (AN) and no increase in abscesses or draining fistulas when compared with baseline (Table 6). [69]

Consequently, the HiSCR serve as a clinical endpoint based on total inflammatory lesion number in a HS patient at that stated moment. Eventually, system let us for the calculation of percentage reductions in abscesses and inflammatory nodules according to beginning as follows: AN50 (50% reduction), AN75 (75% reduction), and AN100 (100% reduction). [2]

Table 6. Hidradenitis Suppurativa Clinical Response

Type of lesions
• Abscesses (fluctuating, draining or not, erythematous, soft or painful to touch/spontaneously painful, round lesion >2 cm) • Inflammatory nodules (solid, erythematous, firm, pyogenic granuloma-like, round lesion <2 cm located in skin or subcutaneous tissue) • Draining fistulae (draining pus on the skin surface)
Response to treatment (compare to baseline)
i. At least 50% reduction in abscesses and inflammatory nodules ii. No increase in the number of abscesses iii. No increase in the number of draining fistulae

2.8.6 Hidradenitis Suppurativa Severity Index

Hidradenitis Suppurativa Severity Index has been used to measure the clinical efficacy of infliximab, an anti-Tumor Necrosis Factor (a-TNF) agent for to treatment of moderate to severe HS in several clinical studies in the past. The system includes objective and subjective categorical factors for assessment. HS Severity Index is not used for routine clinical practice mostly. [70]

2.9. Treatment Guidelines

Even though there is no widely accepted guideline available, there have been several approaches to set standard of care for the treatment of HS. On 2015, European

S1 guideline has been published by Zouboulis C. et al (Figure 4). [56] Guideline consists of comprehensive review of the disease itself and the treatment options by evaluating clinical study results. European S1 guideline is the most accepted and diverse guideline available for HS.

Italian Society of Dermatology and Venereology published a guideline for the use of a-TNFs for HS treatment on 2015 after the European S1 guideline. [71] It is mostly focus on a-TNF agents and refers to European S1 Guideline widely.

On the beginning of 2016, evidence based approach has been published based on the European guidelines (Figure 5). [72] It promotes a holistic evidence-based approach which implemented Level of Evidence and Strength of Recommendation for the treatment of HS due to the need of evidence based treatment guidelines. It is more like a complementary element of the European S1 guideline.

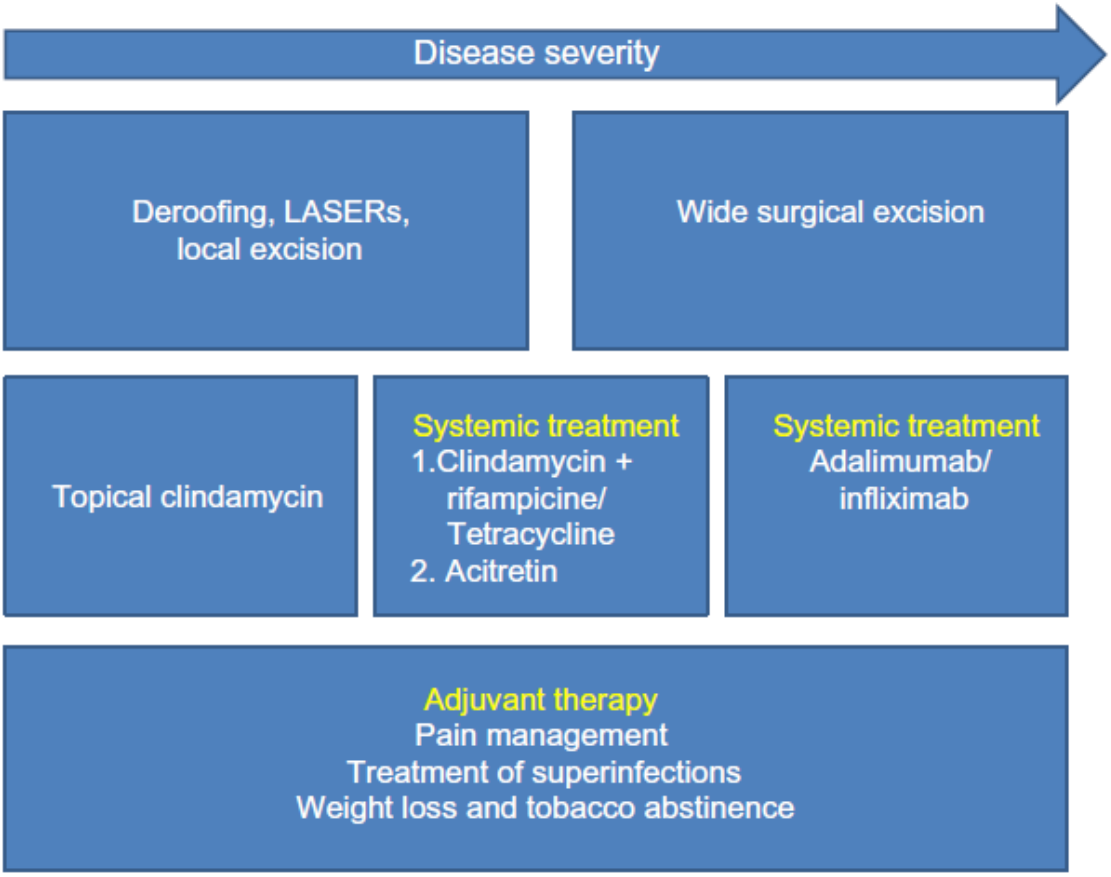


Figure 4. HS Treatment Choices

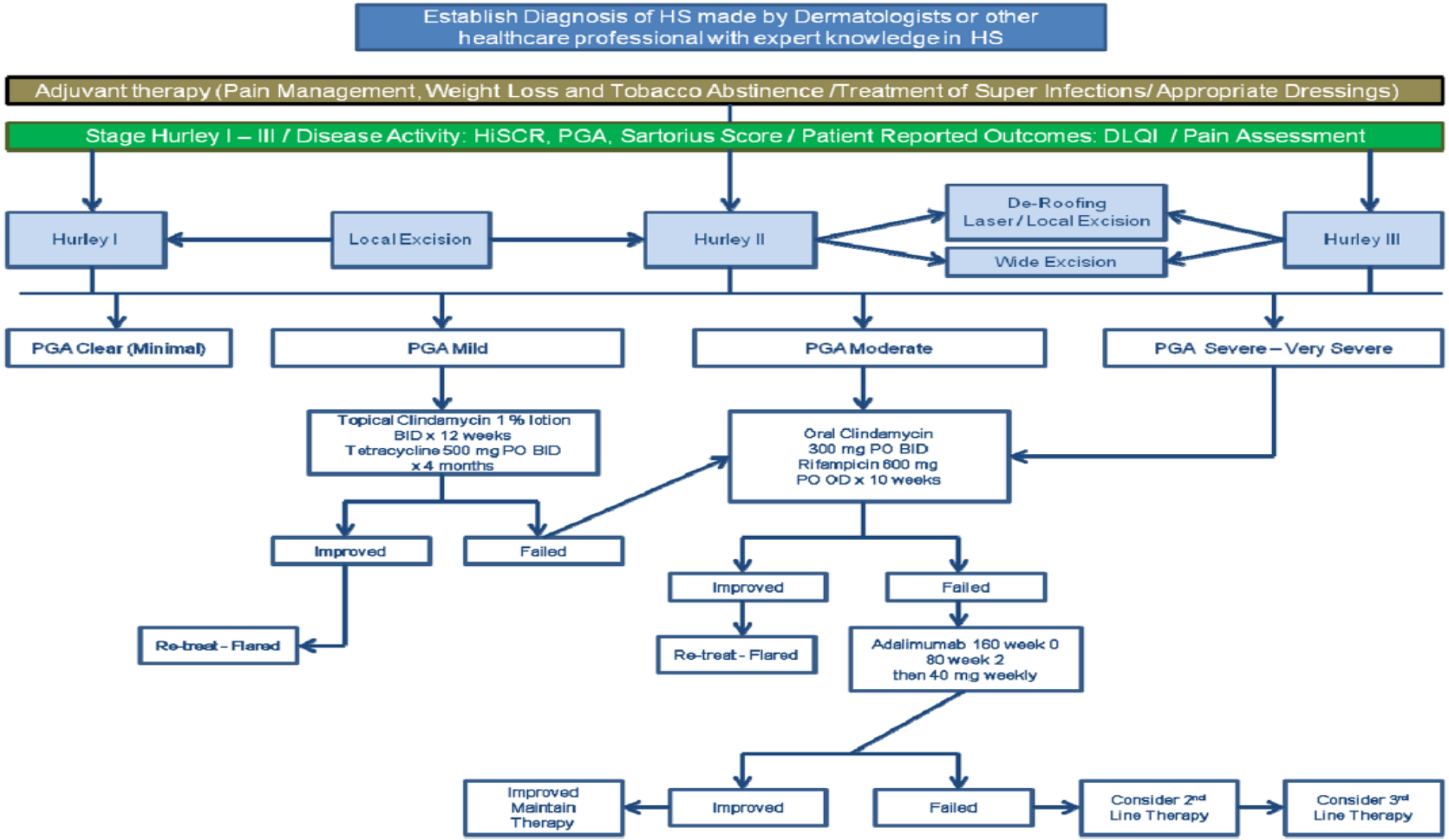


Figure 5. HS Treatment Algorithm

HS: Hidradenitis Suppurativa; HiSCR: Hidradenitis Suppurativa Clinical Response; PGA: Physicians' Global Assessment; DLQI: Dermatology Life Quality Index; BID: Two times a day; PO: Per oral

2.10. Treatment Options

2.10.1 Antibiotic Therapy

Antibiotics are the medicines which most frequently prescribed for the treatment of HS. The efficacy of antibiotics against HS is related in part to their anti-inflammatory affects. [73] There are topical and oral versions of antibiotics available for HS treatment.

2.10.1.1 Topical Clindamycin

Clindamycin is the only antibiotic that has been studied as a topical agent. No data are available on the topical use of any other antibiotics. The European guideline in the management of HS recommended topical clindamycin as first-line therapy for patients with Hurley stage I for 3 months b.i.d..[56] There are few controlled trials available studying the role of topical antibiotics for HS. One study, a small randomized, controlled trial (RCT), found that topical clindamycin has reduced abscess, nodules, and formations. [74]

2.10.1.2 Oral Rifampicin-Clindamycin Combination

The efficacy and safety of oral rifampicin and clindamycin combination in HS treatment has been showed in various case reports with over 140 patients. [75- 78] Definition of the success is varying studies to study but in overall, 80 % of the patients have response to the treatment. According to European S1 guideline, dosage and duration of treatment is recommended as 300 mg b.i.d. given in combination with rifampicin (given either as 1 or 2 doses, 600 mg daily) for 10 weeks. [56]

2.10.1.3 Oral Tetracycline

Topical clindamycin 0.1% b.i.d. has been compared with oral tetracycline 500 mg b.i.d. in a randomized, double-blind, double-dummy clinical trial without finding any difference in both patient reported outcomes (PRO) and the total number of nodules or abscesses. [79] Systemic tetracycline has been commonly used for more largely spread Hurley stage I or mild stage II disease. It has been recommended that, dosage as 500 mg b.i.d. and the duration of treatment as 4 months on the European S1 guideline. It has been stated that the treatment can be prolonged if clinically indicated. [56]

2.10.2 Oral Retinoids

Nowadays evidence of the efficacy of acitretin in the HS treatment is rising and acitretin might be a significant therapeutic option for the treatment of HS. Regardless of the data that showing the limited efficacy of isotretinoin in the HS treatment, isotretinoin is even often preferred for that intention. [73]

It has been stated that acitretin is more efficacious than isotretinoin in the HS treatment. According to Evidence-based approach to the treatment of HS, acitretin has been considered as 2nd line treatment and isotretinoin has not been included to the treatment scale. [72] Acitretin is recommended to use in early stages of HS (Hurley I or mild II) with the daily doses of 0.25–0.88 mg/kg for a period of 3–12 months according to European S1 guideline. [56]

2.10.3 Biologics

Biologic agents which are the proteins derived from human genes have been used for the treatment of inflammatory diseases, such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis and Cohn's diseases for more than 10 years on average. Initial achievement of the biologic agents in the control of those diseases played a role as an impulse to find out the role of biologic therapies in treating HS. [80] Nowadays, biologic agents are progressively been used in the treatment of moderate to severe HS since it has been showed that HS is a chronic inflammatory skin disease. Infliximab and Adalimumab is the most commonly used biologics in the treatment of HS.

2.10.3.1 Infliximab

Infliximab (IFX) is a chimerical antibody constituted of both human and mouse proteins directing for to inhibit TNF-a. IFX targets and neutralizes biologic functions of TNF-a by binding both soluble and transmembrane TNF-a. [80]

Dosage and duration of treatment has been recommended as follow: For maintenance treatment: IFX 5 mg/kg body weight on day zero, two, six and then regularly every 8 weeks. [56]

According to Evidence-based approach to the treatment of HS, IFX has been considered in the 2nd line treatment options and stated that it should use only after failure of adalimumab. [72]

2.10.3.2 Adalimumab

Adalimumab (ADA) is a fully humanized monoclonal antibody that corresponds to the human immunoglobulin G1 and has heavy and light chain variable regions exhibiting specificity for human TNF-a. ADA binds to soluble and membrane bounded TNF-a with a high affinity. [80] Subcutaneous ADA 40 mg every week dosage has been evaluated in two placebo-controlled, randomized, prospective, and double-blind, clinical trials named Pioneer I and II. [67, 81]

ADA is the first drug, which has been approved for the treatment of patients with active moderate to severe HS by regulatory authorities (FDA, EMA etc.), who have failed to respond to conventional systemic treatments. [82]

ADA is recommended moderate to severe HS patients who were unresponsive or intolerant to oral antibiotics as 1st line therapy according to Evidence-based approach to the treatment of HS. Recommended dose and duration is 160 mg at week 0, 80 mg at 2nd week and 40 mg each week thereafter, starting from 4th week. If clinical response with HiSCR is not fulfilled after 16 weeks of treatment, other treatment options such as 2nd or 3rd line treatments must be considered. [56]

2.10.4 Surgery

Surgery is used for the management of patients with moderate to severe HS very common. The sort of surgical intervention determined by the severity and location of the disease and surgical intervention can be small scale or wide and radical. [1]

Most common surgical methods for the treatment of HS are; excision or curettage of individual lesions, deroofing and reconstruction with flap plasty or skin grafting. [56]

Conservative surgical options for milder cases include incision and drainage of abscesses and deroofing of chronic lesions and sinus tracts. Severe HS is treated via limited local or radical wide excision followed by primary closure, healing by secondary intention, flap advancement or grafting. [83] Selection of a wound closure method should be decided by consideration of the size and anatomical region of the defect. [84]

2.11. Comorbid Illnesses

Epidemiological studies suggest that patients with HS present several cardiovascular (CV) risk factors to a higher degree than healthy controls. Tzellos T. et al showed on their recent meta-analysis that HS is associated with CV risk factors which include obesity, diabetes mellitus, metabolic syndrome (MetS), and smoking.[85] Chronic inflammatory diseases such as atherosclerosis, psoriasis, rheumatoid arthritis, and inflammatory bowel disease (e.g. CD, UC), have been associated with a higher risk of CV disorders on several studies. [86, 87]

Egeberg A. et al presented the data of a greater risk of adverse CV results in HS patients who are in correlation with the observance in patients with other chronic inflammatory disorders and endorse the idea that in common inflammatory mechanisms lead to that. Their study showed comparable risk of MI, stroke, major adverse CV events, and all-cause mortality in patients with HS vs those with severe psoriasis, indicating that obesity is unlikely to be a main determinant of the observed association.[88]

The risk of developing MetS can also be linked to obesity and CV. It has been showed that patients with HS have greater chance to have MetS and odds ratio (OR) has been shown as 4.46 for MetS comparing patients with HS and people who don't have HS. [89]

Cancer is also accepted as another risk that HS patients faced. An increase of cancer risk has been reported in patients with HS especially epithelial and non-melanoma skin cancer. [90] Lapins et al showed on their retrospective study consist of 2119 HS patients, the risk of developing any cancer in the cohort with HS were increased as 50%. Non-melanoma skin cancer had the higher risk among the other cancer types. [91]

2.12. Importance of Cost of Illness Analysis

The value of identifying and measuring the costs and results of HS will let to understand more distinctly the financial burden of the disease. The resources used and the potential resources that lost have been identified with the CoI studies. Along with the prevalence, incidence, morbidity and mortality data, CoI studies assist to draw the frame about the effect of a disorder on the public. [92] There are several advantages and disadvantages of CoI studies;

Advantages

- Provide an indication of where healthcare efficiency might be improved by providing a league table of health problems according to their costs
- Provide data to allow later economic evaluation
- Raise consciousness of policy makers to particular diseases, making it more likely that resources will be deployed there in the future
- Provide a single index of the burden of illness

Disadvantages

- Can result in incorrect decisions because they look only at costs and not at costs and benefits
- Risks of bias if methods or data poor or results not fully reported
- Can distort priorities towards high earners and away from the more disadvantaged in cases of the calculation of indirect cost [93]

Determining the total CoI let us know how much society and/or payer is spending on that specific disorder and by implication the amount that would be saved if the disorder were extinguish. On the other hand, it may identify the various elements of the cost and the extent of the contribution of each sector in the society. These data can help to determine research and funding priorities by highlighting areas where inefficiencies may exist and savings can be made. [94, 95]

Knowledge of the CoI can help policy makers to decide which diseases need to be addressed first by health care and prevention policies. Additionally, these studies can indicate for which diseases cures would be valuable in reducing the burden of disease and also reducing costs. [96]

As a result, it is critical to demonstrate CoI studies in order to inform clinical decision making, bring forth new policies and guidelines, and effectively allocate resources accordingly. [93]

3. MATERIALS AND METHOD

This study is a prevalence-based CoI study in focus on direct health care costs from the position of Ministry of Health which means the payer. A multipoint data collection procedure has been done based on the literature search regarding HS epidemiological data, treatment choices and direct health care costs in order to obtain the necessary data for the analysis and the structure of CoI of HS.

A literature search on studies published in English on HS was performed in PubMed with the key words of "Hidradenitis Suppurativa", "Acne Inversa" and "Verneuil Disease" from 1949 to November 2017. All of the titles of the articles and abstracts retrieved from the database using these keywords have been systematically reviewed and analyzed. Disease itself and treatment options have been reviewed comprehensively.

3.1 Prevalence Estimation

Since there is no prevalence studies done in Turkey, several prevalence studies in different scopes (population-based vs. hospital), different time periods (from 1988 to 2017) different diagnosis methodologies (self-reported, medically assessed, diagnosis of treatments codes through automated requests in medical information systems) have been reviewed which is leading to an important variance in estimates and incertitude concerning the actual frequency of HS. According to this variety, the study with the highest number of patients has been choose for the analysis which the prevalence rate is 0.10 %. [11] When to look at the clinical characteristics of the study, HS prevalence among the white race was also determined as 0.10 % which has been assessed as similar to characteristics of Turkish people. Turkish population information has been derived from Turkish Statistical Institute as of 31 December 2016 and used for the analysis. [97] Hurley I, Hurley II and Hurley III variance has been calculated according to the study of Canoui-Poitrine F. et al which assessed the clinical characteristics of 302 French patients with HS. [48]

3.2 Determination of Treatment Approach

Since there is no established treatment algorithm for HS, treatment method derived from both European S1 Guideline [56] and Evidence-based Approach to

Treatment of HS [72] adapted to Turkish healthcare system within the frame of available treatment options.

The costs of hospitalizations, physician office visits (physical examinations), medical and surgical treatments and medical procedures were estimated from the literature and analysis of publicly available health databases. Costs were expressed as of 2017 by using updated Social Security Institution Medical Enforcement Declaration and Republic of Turkey Social Security Institution reimbursement rates and wholesale drug costs. The prices of the available medical treatment options have been derived from RxMediaPharma program.

3.3 Limitations

This study has several limitations and they should be considered along with the results. According to current literature, there is no epidemiological data from Turkey. Accordingly, prevalence data assumed based on the work of Garg et al. [11], and the number of existing HS patients is hypothetically calculated by the relevant data on the population of Turkey. Likewise, the distribution of patients according to the Hurley stages was also calculated on the basis of the study of Canoui-Poitine et al. [48] Since there is no data from Turkey, underestimation or overestimation of the number of patients with HS is possible according to these calculations.

A wide variety of therapeutic options are used in the management of HS patients, as evidenced by current literature. In order to be able to perform an analysis on a structured system, the most ideal and optimal situation which is based on first-line treatment options of the evidence-based treatment algorithm [72] has been considered and the calculations are made by assuming appropriate treatments are used for each Hurley stage. In reality, there might be patients that having the optimal treatments by their staging but also we know that there are patients that are not treating optimally. So it should be highlighted that the result of the analysis is the picture of an optimal situation.

For the surgical interventions, because of the number and types of surgical operations that each patient need will vary, analysis is made with the minimum values and included to the result. Disease itself is unique for every patient and surgical needs will change, therefor it is not possible to reflect the real life situation to the analysis.

The results should be interpreted with the consideration of all these limitations.

4. RESULTS

4.1 Prevalence Estimation

Population of Turkey as of 31 Dec 2016 has been announced as 79 million 814 thousand and 871 people. [97] Total numbers of Turkish people with HS has been estimated as 79.815 (+/- 3.991) with 95% confidence interval according to 0.10 % prevalence rate of Garg and his colleagues' study. [11] Estimated patient number with HS has been shown on Table 7.

Table 7. Estimated Number of Patients with HS in Turkey

Turkey Population	Prevalence (%)	Estimated Number of Patients with HS (with 95% confidence interval)
79.814.871	0.10	79.815 (+/- 3.991)

Among the patients with HS disease, Hurley classification estimation has been done and shown on Table 8. [48] According to that estimation which calculated with the 95% confidence interval, majority of the patients is in the group of Hurley stage I. Number of patients with Hurley stage I, II and III are 54.274 (+/- 2.714), 22.348 (+/- 1.117) and 3.193 (+/- 160) respectively.

Table 8. Patient Distribution According to Hurley Staging

Hurley Stage	Percentage (%)*	Estimated Patient Number (with 95% confidence interval)
I	68	54.274 (+/- 2.714)
II	28	22.348 (+/- 1.117)
III	4	3.193 (+/- 160)

*****Canoui-Poitrine et al. [48]

4.2 Application of Treatment Approach

For moderate and severe HS patients who are planning to have the treatment with biologic agents, opportunistic infections mostly tuberculosis examination has to be done before the initiation of the biologic treatment according to Medical Enforcement Declaration. [98] Cost of the possible tuberculosis examination tests is shown below on Table 9.

Table 9. Tuberculosis Examination List and Costs

Examinations & Procedures	Unit Price
Tuberculosis Examination	
Mycobacterium microscopy	7 TRY/test
Mycobacterium culture	20 TRY/test
Mycobacterium antibiotic susceptibility test	33,90 TRY/test
Lung Graphs	12,80 TRY/test
Thoracic Computer Tomography	55 TRY/test
TOTAL	**128,70 TRY**

Cost of doctor's office visits and hospitalization have been identified according to Medical Enforcement Declaration as both university hospitals and training hospitals. Mean price has been calculated accordingly (Table 10). Primary healthcare services have been excluded due to these healthcare services mostly serve as referral step to the university or training hospitals and they have not been take any role in the management of the disease.

Table 10. Doctor's Office Visits & Hospitalization Costs

	Unite Price (TRY)		**Mean Price (TRY)**
Specialty	University Hospitals	Training Hospitals	
Dermatological and Venereal Diseases	41	33	37
General Surgery or Aesthetic, Plastic and Reconstructive Surgery	55	44	49,50
Hospitalization – Standard bad tariff	30	30	30

Since there is no established treatment algorithm for HS as expressed on the materials and methods section, treatment method derived from current HS treatment guidelines and adapted to Turkish healthcare system within the frame of available treatment options. 1st line treatment options have been used for cost calculation only. 2nd, 3rd line and experimental treatment options have not been taken in to consideration. [72] For the each active substance which is present in the Turkish market, available pharmaceutical preparations have been identified from RxMediaPharma Program and cost of unit dosage has been calculated. By this way, mean cost of the unit dosage has been calculated for each active substance. Treatment durations have been derived from the guideline according to unit dosage of the pharmaceutical preparations and calculated accordingly. Available 1st line treatment options and unit dosage costs have been shown on Table 11.

Table 11. Medical Treatment Options and Cost of Unit Dosages

Drugs	Minimum Price (TRY)	Maximum Price (TRY)	Unit Dosage Price (TRY/mg)
Antibiotics			
Clindamycin	8,31	9,14	0,0035
Rifampicin	4,37	14,88	0,0013
Doxycycline	5,50	6,05	0,0041
Tetracycline	3,61	5, 57	0,0007
Topical Clindamycin	9,53	9,53	0,3177 (TRY/ml)
Anti-TNFs			
Adalimumab	1.186,34	1.186,34	14,82

Medical treatment of patients with HS on Hurley stage I is consist of topical clindamycin 1%, oral tetracycline 500 mg and basic excision of the HS lesions according to evidence based approach treatment algorithm. [72] Recommended treatment duration of topical clindamycin is 3 months and for oral tetracycline, it is 4 months. Cost calculation has been done according to treatment duration recommendations. Surgical treatment has been calculated as 1 time in the treatment frame. Total cost has been calculated as 306,88 TRY for a patient on Hurley stage I (Table 12).

With the same approach, medical and surgical treatment options have been calculated for HS patients on Hurley stage II. Medical treatment is included both topical clindamycin 1 %, oral tetracycline 500 mg and also combination of oral rifampicin-clindamycin 600 mg and adalimumab. [72] Addition to medical treatment, surgical treatment is recommended in a wide range if needed which are excision of the lesions, deroofing, CO2 laser excision, primary and secondary wound closures with flap or grafting techniques. Recommended treatment durations and cost calculation has been shown on Table 13. Total cost for a patient on the stage of Hurley II calculated as 27.631,28 TRY.

For Hurley stage III patients, treatment options are much like patients on Hurley stage II with the exception of the usage of topical clindamycin 1 %, oral tetracycline 500 mg which these treatment options are for milder cases. [72] Surgical interventions remain the same with the Hurley II treatment scheme. Cost calculation has been done according to recommended treatment duration and again, surgical treatment has been calculated as 1 time. As a result, appear similar to the result of Hurley stage II, calculated cost is 27.532,10 TRY for a patient on Hurley stage III. (Table 14)

Table 12. Hurley I Medical & Surgical Treatments and Costs

	Duration	Dosage	Unit Cost	Total Cost
Medical Treatment				
Topical Clindamycin 1%	3 months	twice a day	0,3177 TRY/ml	57,18 TRY
Tetracycline 500 mg	4 months	once a day	0,0007 TRY/mg	42 TRY
Surgical Treatment				
Excision	1	NA	207,70 TRY/session	207,70 TRY
TOTAL				**306,88 TRY**

Table 13. Hurley II Medical & Surgical Treatments and Costs

	Duration	Dosage	Unit Cost	Total Cost
Medical Treatment				
Topical Clindamycin 1%	3 months	twice a day	0,3177 TRY/ml	57,18 TRY
Tetracycline 500 mg	4 months	once a day	0,0007 TRY/mg	42 TRY
Rifampicin 300 mg	10 weeks	twice a day	0,0013 TRY/mg	201,60 TRY
Clindamycin 300 mg			0,0035 TRY/mg	
Adalimumab	Continual*	160 mg at week 0, 80 mg at week 2, 40 mg weekly starting from week 4	14,82 TRY/mg	24.897,60 TRY
Surgical Treatment				
Excision	1	NA	207,70 TRY/session	207,70 TRY
Deroofing	1	NA	400 TRY/session	400 TRY
CO2 Laser Excision	1	NA	550 TRY/session	550 TRY
Primary Wound Closure	1	NA	38 TRY/session	38 TRY
Secondary Wound Closure with Graft	1	NA	400 TRY/session	400 TRY
Secondary Wound Closure with Flap	1	NA	837,20 TRY/session	837,20 TRY
			TOTAL	**27.631,28 TRY**

* According to the PIONEER clinical trial, 68 % of the patients was able to apply the proposed treatment regimen in full, and in 32 % of cases, the treatment was stopped at 12th week. So the average annual dose of Adalimumab has been calculated as 21 boxes with that assumption. [81]

Table 14. Hurley III Medical & Surgical Treatments and Costs

	Duration	Dosage	Unit Cost	Total Cost
Medical Treatment				
Rifampicin 300 mg	10 weeks	twice a day	0,0013 TRY/mg	201,60 TRY
Clindamycin 300 mg			0,0035 TRY/mg	
Adalimumab	Continual*	160 mg at week 0, 80 mg at week 2, 40 mg weekly starting from week 4	14,82 TRY/mg	24.897,60 TRY
Surgical Treatment				
Excision	1	NA	207,70 TRY/session	207,70 TRY
Deroofing	1	NA	400 TRY/session	400 TRY
CO2 Laser Excision	1	NA	550 TRY/session	550 TRY
Primary Wound Closure	1	NA	38 TRY/session	38 TRY
Secondary Wound Closure with Graft	1	NA	400 TRY/session	400 TRY
Secondary Wound Closure with Flap	1	NA	837,20 TRY/session	837,20 TRY
			TOTAL	**27.532,10** TRY

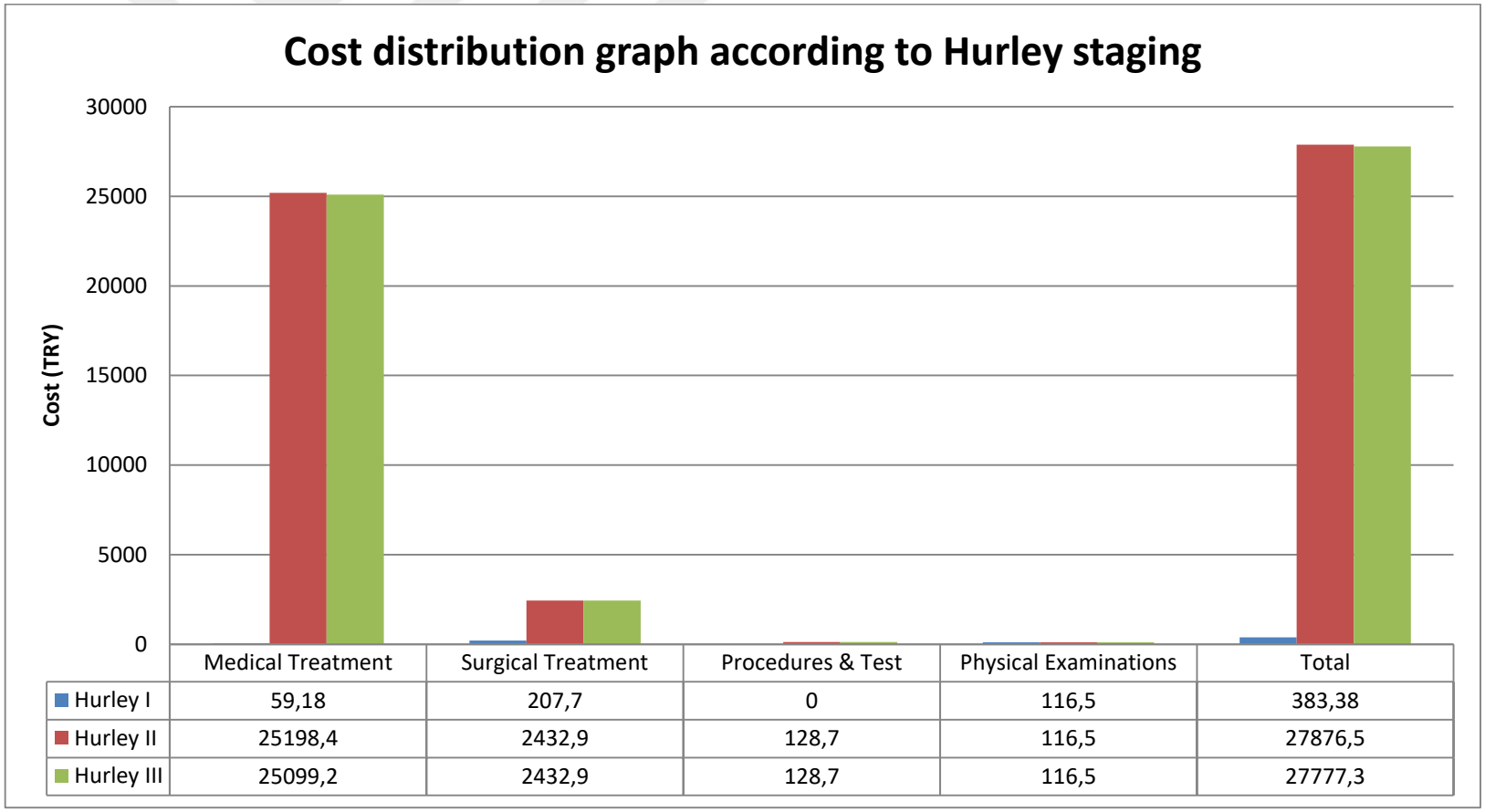
* According to the PIONEER clinical trial, 68 % of the patients was able to apply the proposed treatment regimen in full, and in 32 % of cases, the treatment was stopped at 12th week. So the average annual dose of Adalimumab has been calculated as 21 boxes with that assumption. [81]

If the costs are grouped as medical treatment, surgical treatment, procedures/tests and physical examinations, a total frame can be shown below, on Table 15 for patients with Hurley stage I, II and III. For a HS patient on Hurley stage I, yearly cost is far lower than Hurley stage II and Hurley stage III patients. Direct costs of patients are according to Hurley classification are 383,38 TRY, 27.876,50 TRY and 27.777,18 TRY respectively for one patient and for the year of 2017. Calculation has been shown on Table 15.

Table 15. Cost Calculation

	Cost of stages (TRY)			
	Hurley I	**Hurley II**	**Hurley III**	**Total**
Medical Treatment	59,18	25.198,40	25.099,20	**50.356,78**
Surgical Treatment	207,70	2.432,90	2.432,90	**5.073,50**
Procedures & Test	0	128,70	128,70	**257,40**
Physical Examinations	116,50	116,50	116,50	**349,50**
Total cost (TRY)	**383,38**	**27.876,50**	**27.777,30**	

Same cost calculation has been reflected to the below graphics for to create more visual picture (Figure 6). It has been shown that medical treatments are the majority expenditure of the total cost.



	Medical Treatment	Surgical Treatment	Procedures & Test	Physical Examinations	Total
Hurley I	59,18	207,7	0	116,5	383,38
Hurley II	25198,4	2432,9	128,7	116,5	27876,5
Hurley III	25099,2	2432,9	128,7	116,5	27777,3

Figure 6. Cost Distribution According to Hurley Staging

As a result, the total national cost of HS to the Ministry of Health estimated as 732.477.864,22 TRY (+/- 36.623.893,21 TRY) for the year of 2017 and it is equal to 192.757.332,69 USD (+/- 9.637.866,63 USD) when we exchange the currency to USD as of Nov 13, 2017 (1 TRY=3,8 USD). Details of the cost calculation have been shown on Table 16 in TRY and Table 17 with USD currency. Costs have been shown with 95% confidence interval at parenthetical in each section. It consists of direct medical costs such as medical therapy, surgical treatment, procedures, tests and doctor's office visits (physical examinations).

The 12 months cost were estimated as 20.807.609,17 TRY (+/- 1.040.380,46 TRY) for patients on Hurley stage I, 622.988.590,40 TRY (+/- 31.149.429,52 TRY) for Hurley stage II and 88.681.664,65 TRY (+/- 4.434.083,23 TRY) for Hurley stage III for the year 2017. The largest part of the costs being attributed to medical treatment expenditures and estimated as 646.481.491,09 TRY (+/- 32.324.074,55 TRY).

Table 16. Population Adjusted Cost Calculation with *TRY* (with 95% confidence interval)

	Hurley I	**Hurley II**	**Hurley III**	**Total**
Medical Treatment	3.211.941,96 (+/- 160.597,10)	563.137.972,71 (+/- 28.256.898,64)	80.131.576,41 (+/- 4.006.578,82)	9.298.432,47 (+/- 32.324.074,55)
Surgical Treatment	11.272.733,12 (+/- 563.636,66)	54.370.847,90 (+/- 2.718.542,40)	7.767.263,99 (+/- 388.363,20)	3.287.095,65 (+/- 3.650.542,25)
Procedures & Test	0,00	2.876.208,69 (+/- 143.810,43)	410.886,96 (+/- 20.544,35)	646.481.491,09 (+/- 164.354,78)
Physical Examinations	6.322.934,08 (+/- 316.146,70)	2.603.561,09 (+/- 130.178,05)	371.937,30 (+/- 18.596,86)	73.410.845,01 (+/- 464.921,62)
Total	**20.807.609,17** (+/- 1.040.380,46)	**622.988.590,40** (+/- 31.149.429,52)	**88.681.664,65** (+/- 4.434.083,23)	732.477.864,22 (+/- 36.623.893,21)

Table 17. Population Adjusted Cost Calculation with *USD* (with 95% confidence interval)

	Hurley I	Hurley II	Hurley III	Total
Medical Treatment	845.247,89 (+/- 42.262,39)	148.194.203,35 (+/- 7.409.710,17)	21.087.256,95 (+/- 1.054.362,85)	170.126.708,18 (+/- 8.506.335,41)
Surgical Treatment	2.966.508,72 (+/- 148.325,44)	14.308.117,87 (+/- 715.405,89)	2.044.016,84 (+/- 102.200,84)	19.318.643,42 (+/- 965.932,17)
Procedures & Test	0,00	756.897,02 (+/- 37.844,85)	108.128,15 (+/- 5.406.41)	865.025,17 (+/- 43.251,26)
Physical Examinations	1.663.930,02 (+/- 83.196,50)	685.147,66 (+/- 34.257,38)	97.878,24 (+/- 4.893,91)	2.446.955,91 (+/- 122.347,80)
Total	**5.475.686,62** (+/- 273.784,33)	**163.944.365,89** (+/- 8.197.218,29)	**23.337.280,17** (+/- 1.116.864,01)	**192.757.332,69** (+/- 9.637.866,63)

5. CONCLUSION AND DISCUSSION

To our knowledge, this is the first study in the context of health care utilization and cost for patients with HS conducted in Turkey. Literature search reveal that there are less than thirty manuscripts written about HS from Turkey. Literatures mostly about case reports or series and there is no cost related study among these. When to look at the world literature, there only few studies that aim to find the disease related cost. [15-22]

Kirby and his colleagues find out on their cohort cost-identification study that the majority of the expenditure was the inpatient cost for HS patients. They also compare the results with psoriasis (PsO) patients and resulted that medication costs were higher in PsO group. As a result, emergency department visits and inpatient care shown as the biggest cost source on the study. [15]

In another manuscript which is a follow-through study of Kirby and his colleagues revealed the almost same results with the previous literature. Inpatient costs were the major expenditure for HS patients. The total 5 year cost for the HS patient cohort was found as 23,418,396 USD from the perspective of government health services. HS cohort was consisting of 7,901 patients and for this instance; cost per patient could be calculated as 2.963,97 USD. [16]

Desai and Shah conducted a retrospective cohort study in England for to describe the hospital resource use of patients with HS. They found out that the mean hospital resource utilization cost for a patient with HS was 2.027 GBP per patient per year. But it should be noted that study does not include the details of medication and it is just based on outpatient, inpatient, accident and emergency hospital attendances. [21]

Shalom and his colleagues conducted a study very recently in Israel and they compare the healthcare service utilization cost of HS patients with PsO patients and also with general population. Community clinic visits and inpatient service utilization with drug use data have included to the study. But biologic medications were not available in Israel for the treatment of HS during the study conduction and they were not included to the analysis. As a result, they found out that burden of HS patients were greater than both PsO and general population. There wasn't an estimate on any monetary terms in the study. [20]

The results of our analysis showed that direct cost of patients with HS more than that recognized in Turkey's health care system. Therefore, estimation of the total direct cost attributed to HS is 732.477.864,22 TRY (+/-36.623.893,21 TRY) and revealed that

mean one-year direct cost for one patient is 9.177 TRY (+/- 458 TRY) which can translated as 192.757.332,69 USD (+/- 9.637.866,63 USD) and 2.415 USD (+/- 120 USD) respectively.

Medications seem to be only the definitive important resources funded by the Turkish public health system and if we calculated the contribution margin of the medicines even by patients.

Even though the studies' methods are different, it is possible to compare the results with our study. Cost per patient seems similar between the studies but source and the proportions of the costs were different.

Even though HS is a disease which attributed as 'rare' and 'unknown', it is surprising that it takes an important place in terms of treatment costs.

Here we made an estimation of the economic burden of optimally controlled HS. Intensive pharmacotherapy is required to manage symptoms especially for the patients with Hurley II and III stage; yet, a significant proportion of patients have inadequate control with current treatment regimens according to current literature. Since there is no commonly accepted treatment guideline, physician treatment variety, patient education, and adherence to prescribed regimens remains central issues in achieving control, HS is a heterogeneous condition with variable response to existing therapies.

It is also important to take into consideration the effect of comorbidities (e.g. metabolic syndrome, obesity etc.) on cost of HS and outcomes. This study has been constructed with the data available in the current literature and applied to the Turkish healthcare system.

As highlighted previously, this study has several limitations from different aspects. First of all, lack of epidemiological data from Turkey leads us to use available prevalence data from world literature and adapted to Turkish population. Accordingly, number of HS patients can be over or under estimated. Secondly, 1st line treatment options have been considered only in a variety of treatment options due to the need of a structured analysis. Therefore, an optimal environment has been pictured and calculated. Addition to that, possible direct costs of HS has been discussed widely but the indirect costs are not described and not taken into account in this study.

This CoI study emphases the value of longitudinal HS cohort studies and the study that evaluate how patients receive care throughout the health care system, not only of disease activity. By broaden the point of view even more widely, studies can start to

take into account not only the direct costs to the whole health care system but also the indirect costs resulted from the disease impact on the ability of the patient (and possibly care giver person) to work, and this would address the indirect cost of the disease.

Conflict of Interest

I declare that I am working as an employee at AbbVie Inc. which is the producer and owner of one of the therapeutic options that are using for the treatment of moderate to severe Hidradenitis Suppurativa.

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Bachelor	Pharmacy	Ankara University, Turkey	2012
Bachelor	Pharmacy	Universidad Complutense de Madrid, Spain	2009
High school	Science	Mersin Science High School, Turkey	2006

Foreign Languages	**Foreign Language Exam Result**
English	-
Spanish	-

Job Experience

Job Title	**Institution**	**Duration**
Medical Manager	AbbVie, Turkey	2016-Present
Medical Scientific Liaison	AbbVie, Turkey	2015-2016
Clinical Research Associate	AbbVie, Turkey	2014-2015
Clinical Research Associate	Atlas Medical Services, Turkey	2013-2014
Clinical Trial Assistant	GlaxoSmithKline, Turkey	2010-2012

(Long Term Trainee)		
Sales Associate, Work & Travel Program	Konad Nail Art Inc, USA	Jun 2008-Sep 2008

Computer Skills

Program	**Level of skill**
Microsoft Word	Very Good
Microsoft Power Point	Very Good
Microsoft Excel	Medium