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Arguments for a national questionnaire-based screening for hidradenitis suppurativa in Denmark

Peter Theut Riis[1], Pernille Lindsø Andersen[1]✉, Gregor Borut Jemec[1]

Abstract

Introduction: Hidradenitis suppurativa (HS) is a chronic inflammatory disease. HS patients develop painful subcutaneous nodules, primarily in the intertriginous regions. Early diagnosis is crucial to initiate appropriate treatment, which may prevent disease progression. The cost of treatment increases with disease severity. Studies have found a considerable diagnostic delay in HS. Screening programs may reduce diagnostic delay and allow for better utilization of resources.
Methods: Arguments for implementing an HS screening program were explored based on the 10 WHO criteria for implementing screening programs.
Results: HS is an important health problem due to its prevalence and the adverse effects of the disease. Facilities for treatment and diagnosis exist, and the validated screening questionnaire is considered acceptable to the population. HS patients should be seen by a dermatologist and treated accordingly. Medical expenses increase with disease severity, and finding patients with early-stage HS is considered cost-effective.
Conclusions: We consider a screening program as valuable for public healthcare. Patients can avoid extensive surgery or treatment with biologics if disease progression is prevented, and this will reduce medical expenses for the public healthcare system. Politicians should consider implementing a screening program for HS.

Keywords: screening, hidradenitis suppurativa, acne inversa

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Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease. Patients suffering from this disease recurrently develop painful subcutaneous nodules, primarily in the intertriginous regions; for example, the axilla and the groin (1–3).

In approximately 60% of patients, the majority of the inflammatory nodules progress to abscesses, or pus-filled cavities that drain laterally through cutaneous tunnels to the surface of the skin (4, 5). The cutaneous tunnels heal with scarring, and during the repeated cycles of inflammation, abscesses, and scarring permanent draining fistula gradually begin to mar the skin.

The presence of permanent cutaneous tunnels predisposes patients to further inflammation, more scarring, and more tunnels, in what becomes a vicious cycle.

The disease affects females three times as often as males, and the disease is associated with smoking and obesity. Smoking is associated with the presence of the disease, and also with more advanced disease stages (6–14). Several studies have shown that obese people suffer from HS more often and that obese HS patients tend to have more severe disease than non-obese patients. In addition, remission is less likely for obese patient (8, 10, 12, 15–19).

To combat the disease, dermatologists rely on three avenues of care: reducing inflammation with anti-inflammatory systemics or topical medication (20–27), surgical removal of tunnels and fistula (1, 28–31), and adjuvant therapy in the form of weight reduction and smoking cessation (1, 32).

Many patients are misdiagnosed by their general practitioner due to the clinical presentation of HS and its similarity to simple abscesses. The taboo of having an abscess, a disease entity associated with uncleanness, prevents many from contacting a general practitioner in the first place (33). For HS, the diagnostic delay is on average 7.2 years, compared to 1.6 years for psoriasis (33). Screening the general population or part of it might be a way to reduce this delay. The cost of treating HS increases with increasing duration of the disease because the patients accumulate scar tissue over time, as explained above (34). In addition to reducing the diagnostic delay, screening will allow for better utilization of healthcare resources due to the cheaper lifetime treatment cost for patients that start treatment early.

Table 1 | **World Health Organization recommendations for screening programs.**

No.	Criterion
1.	The condition should be an important health problem.
2.	There should be a treatment for the condition.
3.	Facilities for diagnosis and treatment should be available.
4.	There should be a latent or early symptomatic stage.
5.	There should be a test for the condition.
6.	The test should be acceptable to the population.
7.	The natural history of the disease should be adequately understood.
8.	There should be an agreed policy on who to treat.
9.	The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10.	Case-finding should be a continuous process, not just a “once and for all” project.

[1]Department of Dermatology, Zealand University Hospital, Roskilde; Health Sciences Faculty, University of Copenhagen, Copenhagen, Denmark. ✉ **Corresponding author: pernille.lindsoe.andersen@gmail.com**

Methods

The World Health Organization has established 10 criteria for implementing a screening program; see Table 1 (35). Each criterion for implementing a screening program was examined in the context of HS to determine whether a HS screening program may be recommended.

Results and discussion

1. The condition should be an important health problem.

The importance of any medical condition as a health problem arguably rests on two pillars. One is how adversely patients are affected by the condition. The second is the prevalence of the condition in the general population. As outlined above, HS is a very distressing condition.

Adverse effects

Pain

Patients with HS reported the highest pain scores when compared to psoriasis, skin tumors, eczema, acne, and other skin diseases (36). A study of 4,010 dermatological patients and 1,359 controls focusing on Health Related Quality of Life (HRQoL) using the EuroQol 5-Dimensions (EQ5D) tool found that, of all skin conditions, HS was the one most associated with the pain/discomfort domain (37).

The same study found HS patients to have among the three lowest possible utility scores using EQ5D with a mean score of 56.9, surpassed only by leg ulcers (56.0) and prurigo (56.5). However, a linear regression showed that HS had the most impact on self-reported quality of life on a visual analogue score HRQoL measurement included in the EQ5D, after adjusting for confounders (37). When asking patients how HS affects their lives, social isolation and feelings of dependency are common themes (38). They feel unloved and unworthy of love due to scarring and inflammation (38).

Quality of life

Several tools have been employed to measure the quality of life for patients with HS. Instruments range from the dermatologically focused Dermatologic Life Quality Index (DLQI) (39) to more general tools such as the Short Form-36 (SF-36) (40). Patients have significantly decreased quality of life (QoL), regardless of the tool used (38, 41–45). Several of these studies also demonstrate that QoL decreases as the disease advances through Hurley stages (41–44).

Depression

HS patients are prone to depression and score higher on depression instruments such as the Major Depression Inventory (36, 46) and Hospital Anxiety and Depression Scale than healthy controls (47). Questionnaire-based studies find that between 9% and 39% of patients suffer from depression, with higher scores correlated with disease severity (42, 48).

Co-morbidities

HS is associated with several comorbidities, some related to metabolic syndrome, such as obesity, hypertension, dyslipidemia, and diabetes (17–19, 49), but also thyroid disorders, psychiatric disorders—especially within the affective spectrum—acne, polycystic ovarian syndrome, lymphoma, drug dependence, and squamous cell carcinoma (9, 12, 16, 49).

Professional activity

Because HS often debuts in patients' early 20s, it affects the active years in which people usually take part in education and establish themselves on the job market. This may be part of the reason for the low socioeconomic status of HS patients (50). The acute disability associated with disease flares significantly increases absenteeism and can prove a barrier for promotion or advancement (43). A Danish survey of hospital-recruited HS patients (n = 215) found that 25.1% of non-retired, non-student HS patients were currently unemployed. This is a significant difference from the national average of 6.2% (51).

Prevalence

Several studies have addressed the issue of prevalence, the second pillar of the importance criterion. However, given the scope of this article, prevalence studies conducted in Denmark are the focus of this discussion.

Two smaller studies determined the prevalence of HS to be 4% (52) and 4.1% (53), respectively. However, one article examined young adults at a clinic for sexually transmitted diseases (53) and the other used an unvalidated questionnaire distributed to nurses (52). Population studies have estimated the prevalence to be between 0.97% (54) and 2.1% (13) using an unvalidated (54) and validated questionnaire (13), respectively (55). For comparison, a recent study found a prevalence of 2.2% for psoriasis in Denmark (56).

No Danish incidence studies have been conducted, but an American study found an incidence of 6.0 (95% CI: 5.2–6.7) per 100,000 person-years, with up to 18.4 per 100,000 person-years in females aged 20 to 29 (12). Studies of prevalence in the United States found a lower prevalence than Danish studies—namely, between 0.05% and 0.20% (57–60)—which must be considered when extrapolating the American incidence to the Danish population.

2. There should be a treatment for the condition.

Several treatments exist for HS, but none of them are uniformly effective and several attempts are often needed to find a treatment suitable for an individual patient. In general, topical treatments are employed as a first-line treatment, followed by prolonged antibiotic courses as a second-line treatment, using biologics only if antibiotic therapy fails. Permanent scar tissue from repeated flares necessitates surgical intervention, which removes large areas of flare-prone skin (1).

Evidence-based topical treatments include resorcinol (20), clindamycin (22, 25), and intralesional triamcinolone injections (61). If topical treatments are unable to control inflammation, systemic therapies are added.

For systemic therapy, the European guidelines recommend tetracycline (25) and a combination of clindamycin and rifampicin (24, 62, 63) as the go-to drugs for reducing inflammation (32). Several other anti-inflammatory drugs such as corticosteroids (64, 65), dapsone (66–68), and ciclosporin (69, 70) can be employed (32) before trying biologic treatments; however, the evidence level is unsatisfactory (71).

Adalimumab (26, 27, 72, 73), anakinra (74), and ustekinumab (75) have all shown promising results for the treatment of HS. The evidence level is higher for adalimumab (76), which is currently the only drug with HS as a registered indication.

Surgical intervention is needed to treat the scarring and tunnels formed by HS (77). Although extensive surgery is indicated in

widespread disease and results in a low recurrence rate (78), the procedure can be disfiguring (77). More localized surgical methods have a better cosmetic outcome, but they have higher rates of recurrence (61).

Incision and drainage can be employed for immediate pain relief if an abscess is present, but solid inflamed tumors obviously should not be incised (79, 80). The tissue-saving surgical technique, deroofing, utilizes a probe to explore the extent of cutaneous tunnels and subsequently removes the roof of these tunnels (81).

Skin-Tissue-sparing Excision with Electrosurgical Peeling (STEEP) sequentially removes layers of the skin until healthy tissue is reached in order to preserve the maximum amount of healthy tissue (82).

Wide excision includes a margin of disease-free tissue and can be extensive. The surgical defects are closed with various techniques, including a split-thickness skin graft or flaps, but are occasionally left to heal by secondary intention, where the wound is left open and heals by granulation (28, 77, 83–86).

Treatment algorithms are beyond the scope of this article, but they are extensively covered in the European S1 guidelines (32) and in a recent review by Saunte et al. (77).

3. Facilities for diagnosis and treatment should be available.

A potential screening program should primarily allocate resources to private dermatologists, but to surgical specialists as well. Private dermatologists are able to diagnose and manage the majority of HS patients. Extensive surgery can be performed by a combination of private or hospital-based dermatologists, plastic surgeons, gynecologists, and abdominal surgeons, depending on the location of scarring. The facilities needed exist and treatment is available as discussed above, but both will obviously require funding to handle an increase in HS patients.

4. There should be a latent or early symptomatic stage.

HS can be divided in three so-called Hurley Stages (87), created to identify the level of scar tissue in a single region. Hurley I is defined as abscess formation, single or multiple, without sinus tracts or cicatrization; Hurley II is characterized by recurrent abscesses with tract-formation and cicatrization, single or multiple, widely separated lesions; and Hurley III is defined as diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

Because scar tissue is permanent, patients can progress through the Hurley stages, but they can never regress without surgical intervention. Assessment of a patient's surgical needs is easily performed by using the Hurley classification system because patients categorized as Hurley II and III require surgery. Therefore, Hurley stage I is a perfect example of an early symptomatic stage.

Prevalences of the three stages have only been examined in a hospital setting, skewing the distribution toward the severe spectrum (16, 88). A hospital-based sample reported 68.2% Hurley I, 27.6% Hurley II, and 3.9% Hurley III patients (16).

5. There should be a test for the condition.

A validated two-stage questionnaire was developed by Vinding et al. in 2014 (13). Because patients generally refer to the lesions of HS as boils, the initial question is phrased: "Have you had an outbreak of boils during the last 6 months?" If responders answer affirmatively, they are presented with the follow-up question: "Where and how many boils have you had?" with five different location options listed (axilla, groin, genitals, under the breasts, and other locations) (13). If patients answer "yes" to the initial question and report two or more boils in the follow-up question, responders can be categorized as suffering from HS.

This test has a sensitivity of 90%, a specificity of 97%, a positive predictive value of 96%, and a negative predictive value of 92% (13). We suggest distributing the questionnaire to the population or part of the population and instructing responders with a positive response to visit their private dermatologist for confirmation.

6. The test should be acceptable to the population.

The questionnaire can be distributed online and takes less than 2 minutes to answer. In the Danish context, the state-issued e-mail address can be used. Individuals that do not have such an e-mail address (less than 10% of the population) can receive the questionnaire by mail and answer on paper.

The disease is not well known, and from anecdotal experience most patients react with a chuckle when answering the questionnaire, making it unlikely to induce fear of developing the disease at a later stage. Before starting nationwide screening, the psychological effect of the questions should be explored properly.

7. The natural history of the disease should be adequately understood.

HS is a disease of the hair follicles. Infundibular keratosis and hyperplasia of the follicle epithelium cause occlusion of the hair follicle (89–92). The accumulation of debris gives rise to the formation of a cyst and later to rupture of the follicle (93, 94). The introduction of follicle content into the dermis causes a massive inflammatory response. The inflammatory cytokines present in HS lesions are still under investigation. So far, increased levels of tumor necrosis factor-α (TNF-α) (95–97) and interferon-γ (98) along with increased levels of several interleukins (IL) have been found. IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17A, IL-20, IL-22, IL-23, IL-24, IL-26, IL-32, IL-32α, IL-32β, IL-36α, IL-36β, and IL-36γ have been examined and found to be increased compared to controls (95, 97–105).

Histologically, the disease is characterized by a lymphocytic infiltrate and the subsequent loss of sebaceous glands. The later stages of the disease often present an infiltrate of neutrophils, monocytes, and mast cells (95, 105, 106).

The disease typically debuts in the early 20s (9, 107) and is considered chronic. A study has showed that 39.4% of patients experienced remission after a mean of 22 years (8). This finding is supported by a population survey that showed that, as age increases, the prevalence decreases correspondingly (13). In general, disease severity tapers off around the age of 55, although activity can persist for far longer (9, 14).

8. There should be an agreed policy on who to treat.

The suggested screening questionnaire was developed based on the disease definition accepted at the HS foundation meeting in Dessau and modified in San Francisco in 2009 (13). The following three criteria must be met: 1) typical lesions (i.e., deep-seated painful nodules, or "blind boils" in early lesions) and abscesses, draining sinus, bridged scars, and "tombstone" double-ended pseudo-comedones in secondary lesions; 2) typical topography (i.e., axillae, groin, perineal region, buttocks, and infra- and intermammary folds); and 3) chronicity and recurrences.

The screening questions cover all three criteria; recipients can, however, incorrectly identify non-boil lesions as boils, but

the questionnaire is validated with high sensitivity and excellent specificity (13). We suggest that all patients identified as HS patients should be seen by a dermatologist for confirmation and treatment.

9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.

The balance between the cost of identifying a case and the associated medical expenditure as a whole will depend on the country. In Denmark, more than 90% of Danes are in the "e-boks" e-mail system (108), a personal e-mail account linked to the unique Danish Civil Registration system, which supplies each Dane with an identification number. This allows for easy e-mail access to the majority of Danes. The e-boks system is currently utilized by the Danish Hospital system when communicating with patients. Patients that have not agreed to use e-boks still receive all communication in an analogue paper format. Using the infrastructure already in place and sending the questionnaire in an online format makes screening the adult population a low-cost endeavor.

Early treatment of lesions to prevent the formation of inflammation-inducing scar tissue is of paramount importance in managing the disease, both from a patient perspective and an economic perspective (34). The more severe the disease, the more expensive it is to treat. The cost of surgery increases the more extensive the area, and the biologic medication used to treat the most severe inflammation is notoriously expensive.

A British study estimated that patients with an ICD10 code of L73.2 (HS) as a primary diagnosis had a mean hospital utilization cost of £2,027 (~ €2,300) per year, with the highest cost for surgery (109). In Denmark, patients cost even more because the state pays the additional cost for medication if the total yearly expense of all medication exceeds €537 (110). Three months of treatment with tetracyclin costs €108 (111), and a combination treatment of rifampicin and clindamycin costs €266 (112, 113).

Most patients use these medications more than 3 months per year, and added to that comes the cost of topical treatments, bandages, painkillers (114), and other medicine. Recall that the psychiatric comorbidities increase with severity (41–44), and that these patients are prone to depression, and there is also the cost of potential anti-depressants as well as other psychiatric therapies. In our experience, most HS patients receive financial support for their medication.

Adalimumab, the only registered drug for HS and the most widely used biologic, has a market price of €2,975 for 14 days of treatment, which corresponds to €38,680 per year. Adalimumab is dispensed by and paid for in full by the hospital. In addition to medical expenses, public healthcare also covers the full cost of a visit to the dermatologist if the referral is of a non-cosmetic character.

The cost of HS patients in Denmark has never been examined in full, and the benefit of a screening program cannot be accurately calculated before actually implementing it. We can, however, venture an educated guess. We suggest sending the screening questionnaire every 5 years to adults aged 18 to 40. Patients screened positive are referred to either a private dermatologist or a hospital-based dermatologist for confirmation and treatment.

For the total account of the calculation, see Supplementary Table 1. The entire screening process is estimated to cost approximately €422,932. In perspective, that is only slightly above the cost of keeping two patients on adalimumab treatment for a 5-year period (€386,800). If the screening program can prevent at least two patients from reaching the last-line-treatment of adalimumab for 5 years during their lifetime, it will already be cost-effective, and added to that are the secondary financial benefits of early diagnosis.

10. Case-finding should be a continuous process, not just a "once and for all" project.

As described above, we suggest screening the population every 5 years. Assuming an incidence of 5.2 to 6.7 per 100,000 person years (12), approximately 1,013 to 1,305 new cases will develop after 5 years, making subsequent screenings slightly less expensive.

Conclusion

Whether the criteria for initiating screening for HS are fulfilled is a matter of interpretation and a political point of view. The far-ranging effect of a screening program is impossible to predict before implementing it, but in our humble estimation a screening program will be of significant benefit to patients and to public healthcare as a whole. It is reasonable to suggest that a screening program for HS would be cost-effective and in the long run would free up healthcare resources to be utilized elsewhere. In conclusion, politicians should consider implementing a screening program for HS.

Conflict of interest

PTR and PLA declare no conflict of interest. GB Jemec has received honoraria from AbbVie, Coloplast, Pfizer, Pierre Fabre, Inflarx, MSD, Novartis, and UCB for participation on advisory boards, grants from Abbvie, Leo Pharma, Novartis, Janssen-Cilag, Regeneron, UCB, and Sanofi for participation as an investigator, and speaker honoraria from AbbVie, Galderma, and Leo Pharma.

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