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Hidradenitis Suppurativa: Identification, Assessment and Treatment

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Independent expert commentary provided by Associate Professor Saxon Smith and Professor George Braitberg

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This publication is intended as an educational resource for healthcare professionals, particularly those who may encounter hidradenitis suppurativa/acne inversa (HS) in an acute setting. It aims to assist with identification of the disease, and reviews the available treatments, both pharmacological and surgical. Particular emphasis is given to adalimumab, the only pharmacological treatment with registered approval for HS.

Introduction

HS is a painful, chronic inflammatory skin disease characterised by multifocal, recurrent nodules, abscesses and fistulae, predominantly affecting the axillary, inguinal, breast-fold and anogenital regions.[1] HS ranges from localised lesions (mild disease) to multiple areas of widely dispersed lesions, including interconnected sinus tracts and hypertrophic scars (severe disease).[2] The disease has profound physical and psychological consequences that affect quality of life.[3] Early disease-modifying intervention is often hampered by poor recognition of the disease, with an average time interval of 7.2 years from symptom onset to diagnosis.[4] A range of treatments are available, but high-quality evidence is lacking for many of them.[5,6,7] The anti-TNF-α monoclonal antibody adalimumab is the first and only pharmacological treatment to be approved by regulatory authorities for HS.[8] In Australia, it is available through the Pharmaceutical Benefits Scheme, when prescribed by a dermatologist to patients with moderate to severe disease and an inadequate response to antibiotics.[9]

Pathophysiology, risk factors and comorbid conditions

The central pathogenic event in HS is believed to be follicular occlusion. Infundibular hyperkeratosis of the terminal follicles and hyperplasia of the follicular epithelium result in the collection of debris, cyst formation, rupture, sinus tract formation and ultimately, scarring.[10] Disruption of the hair follicle produces an inflammatory response,[10] and increased levels of interleukin-1β, tumor necrosis factor-α and interleukin-10 have been found in HS lesions.[11] Factors contributing to this inflammation include the patient's genotype and smoking status, obesity, adipokine dysregulation, insulin or glucose dysregulation, the microbiome and environmental factors.[12]

Approximately one third of patients with HS have a positive family history of the disease, and an autosomal dominant inheritance pattern has been suggested.[13] Prevalence of smoking in patients with HS has been estimated at 42-90% and has been associated with increased severity of HS.[14,15,16] Nicotine may lead to follicular plugging via promotion of hyperplasia of the follicular infundibulum and oversecretion of eccrine glands, or contribute to inflammation via induction of neutrophil chemotaxis.[17] The prevalence of obesity in patients with HS is 60-88%.[16,18,19] Obesity is associated with HS disease severity, and weight loss can lead to clinical improvement.[20] Likely mechanisms linking chronic inflammation and obesity include effects on the skin and microbiome, and mechanical friction.[12,21]

Patients with HS have an increased prevalence of the metabolic syndrome compared with the general population, which is thought to be due to the proinflammatory state.[12] Vekic et al. report high rates of dyslipidaemia (44%), insulin resistance (42%), diabetes (17%) and hypertension (16%) in patients with HS treated at the Liverpool Dermatology Clinic in New South Wales, Australia.[12] The high prevalence of polycystic ovary syndrome in female patients with HS (30% at the Liverpool Dermatology Clinic) suggests an association with the endocrine system.[12]

HS is clearly associated with autoinflammatory diseases such as Crohn's disease and spondyloarthropathies, raising the possibility of a shared pathogenesis.[12, 22] Follicular occlusion diseases such as nodulocystic acne, pilonidal sinus and keratosis pilaris are also closely associated with HS.[12,22]

Epidemiology

Estimates of global prevalence of HS range from 1-4%, similar to the prevalence of psoriasis, meaning HS cannot be considered a rare disease.[23,24] In Australia, prevalence of HS has been estimated at 0.67%.[25] Females are three times more likely to develop the disease than males.[23,24]

Onset of HS most commonly occurs in patients aged in their early 20s, and is typically active during the third and fourth decades of life.[23,24] However, the disease can occur at any age, including prepubertal children.[5,26] Disease onset before the age of 13 years has been reported in 7.7% of patients with HS, and is associated with stronger genetic susceptibility and more widespread disease.[5,27]

Consequences of disease

Pain is reported by almost all patients with HS, and is the most significant factor contributing to impaired quality of life.[3,23] Quality of life in patients with HS has reported to be lower than that of patients with other burdensome skin diseases such as psoriasis and atopic dermatitis.[28,29]

Depression is significantly associated with HS, with a prevalence of up to 39% reported in cross-sectional studies.[29-33] Patients with HS are also at increased risk of anxiety, social isolation, poverty, family deterioration and suicide.[3,34,35] A European multicentre, cross-sectional study reported impairment of sex life in 67% of patients with HS.[36]

Patients with HS have a higher unemployment rate than the general population.[35,37] Among employed patients, approximately half have taken sick days because of HS, on average 14-33.6 days per year.[30,32] Jemec et al. reported that patients with HS lost an average of 2.7 workdays per year, but those with severe disease were unable to work at all.[38] A large UK study of Hospital Episode Statistics data found a high burden of hospital attendances for patients with HS, who were predominantly of working age.[39] In a large US study of MarketScan medical claims, rates of hospitalisation and emergency department use were higher in patients with HS compared to those with psoriasis.[40]

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HS remains a complex and evolving pathophysiology. It is clear that cytokines such as TNF-α, IL-10 and IL-17, are key players. However, it is less well understood why this inflammatory condition is triggered. There are distinct associations including obesity, smoking and polycystic ovary syndrome. And yet, there appears to be significant ethnic diversity in gender predisposition. In Caucasian predominant Western populations, females are at least twice as likely to suffer the condition. Whereas, in Asian countries such as Korea and Japan it is more common in males.

HS is a devastating condition for those who suffer it. It is painful, pungent and unpredictable. Therefore, it is not surprising that people who suffer HS have a significant impairment in quality of life and higher rates of depression and anxiety.

Diagnosis

HS is often not recognised and/or may be misdiagnosed by healthcare professionals.[4,41] Patients may present to a variety of healthcare providers and be subjected to repeat and unnecessary investigations and procedures.[41] The diagnosis of HS should therefore be made by a dermatologist or other healthcare professional with expert knowledge of the disease.[5]

Diagnosis requires 3 criteria to be fulfilled:

- Typical lesions (painful nodules, sinus tracts, abscesses and/or scarring) are present
- Typical distribution of lesions (axillae, groins, perineal and perianal regions, buttocks, infra-mammary and inter-mammary folds)
- Chronicity and recurrence of lesions (≥2 episodes in a 6-month period).[5,42]

Examples of typical HS lesions in the axillar, breast and buttocks are shown in **Figures 1a, 1b** and **1c**.

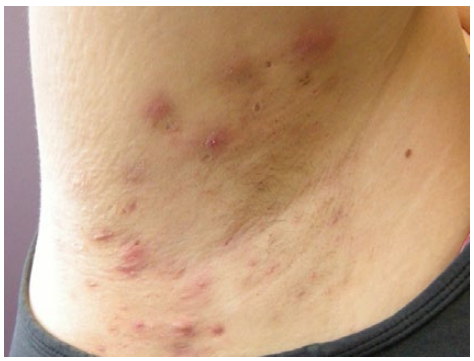

Figure 1a. Axillar HS lesions
(image supplied by AbbVie).

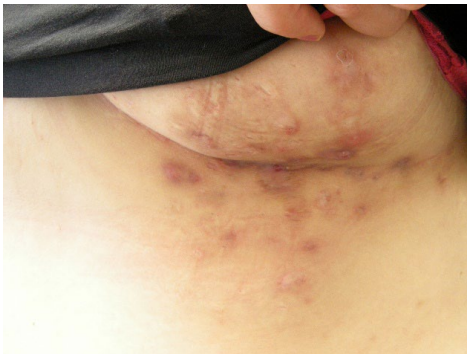

Figure 1b. Breast HS lesions
(image supplied by AbbVie).

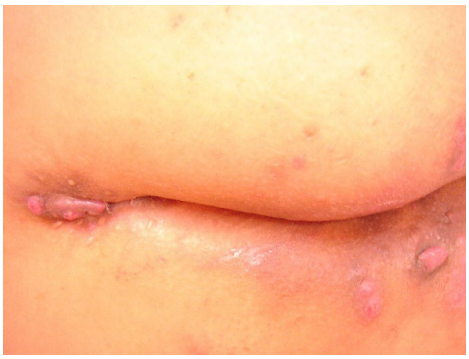

Figure 1c. Buttocks HS lesions
(image supplied by AbbVie).

Secondary diagnostic criteria for HS include a family history of the disease and an absence of pathogens at lesional sites.[42]

Differential diagnoses include staphylococcal infection, cutaneous Crohn's disease, simple abscesses, neoplasms, lymphogranuloma venereum, cutaneous actinomycosis and the scrofuloderma type of cutaneous tuberculosis.[42]

Assessment

Clinical assessment of HS severity can be achieved using Hurley staging, the HS-Physicians Global Assessment (HS-PGA) and the modified Sartorius score.[12,42] The Hurley classification is the most widely used of these scores and is useful for the determination of 3 disease severity groups (see **Table 1**), but as a static score it is not suitable for monitoring disease changes with treatment, particularly the inflammatory component of HS.[5,42]

Table 1. Hurley classification of HS disease severity.[5,42]

Hurley stage	Description
I	Abscess formation, single or multiple, without sinus tracts and cicatrisation
II	Recurrent abscesses with tract formation and cicatrisation, single or multiple, widely separated lesions
III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area

The HS-PGA is a dynamic, 6-stage tool which can be used to assess both disease severity and clinical improvement with pharmacological treatment (see **Table 2**).[42,43] However, marked heterogeneity can exist amongst patients in the most severe category, meaning that some patients may experience clinically important improvement without a meaningful reduction in HS-PGA score.[43]

Table 2. HS-PGA classification of HS disease severity.[42,43]

HS-PGA	Description
Clear (score = 0)	No inflammatory or noninflammatory nodules
Minimal (score = 1)	Only the presence of noninflammatory nodules
Mild (score = 2)	<5 inflammatory nodules *OR* 1 abscess or draining fistula and no inflammatory nodules
Moderate (score = 3)	<5 inflammatory nodules *OR* 1 abscess or draining fistula and ≥1 inflammatory nodules *OR* 2-5 abscesses or draining fistulae and <10 inflammatory nodules
Severe (score = 4)	2-5 abscesses or draining fistulae and ≥10 inflammatory nodules
Very severe (score = 5)	≥5 abscesses or draining fistulae

The modified Sartorius score involves counting individual nodules and fistulae, but the fact it includes lesions insensitive to pharmacological treatment, such as scars, is a limitation when assessing treatment effectiveness.[42]

A newly developed, dynamic assessment tool called the Hidradenitis Suppurativa Clinical Response (HiSCR) has been developed and validated in randomised controlled trials of adalimumab.[8,44,45] The HiSCR considers the status of 3 types of lesions: abscesses (fluctuant, with or without drainage, tender or painful); inflammatory nodules (tender, erythematous, pyogenic granuloma lesion); and draining fistulae (sinus tracts, with communication to skin surface, draining purulent fluid).[44] Response to treatment using the HiSCR is defined as a ≥ 50% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count.[44]

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On average patients with HS have a delay to diagnosis of 7 years. Over this period, they will see many different doctors and even present to emergency department with the misdiagnosis of 'chronic boils'. Furthermore, this leads to frequent use of antibiotics due to a misunderstanding that this is an active infection rather than the chronic inflammatory condition we now understand it is. Painful abscess and cysts can appear overnight or can be chronic discharging sinuses. However, there is a strong clinical predilection of lesions to axillae, inframammary, intra-abdominal apron, and groin/buttocks. This is a consistent feature which should tip off HS as a possible differential diagnosis. The presence of double headed comedones is almost a pathognomic feature of the condition and should be searched for when patients present with 'chronic boils'. Furthermore, swabs taken for microscopy, cultures, and sensitives frequently fail to demonstrate a pathogen.

Treatment

Guidelines for the treatment of HS were published by the European Dermatology Forum in 2015.[42] Based on these guidelines and considering the strength of evidence for various treatment strategies, researchers from the European Hidradenitis Suppurativa Foundation developed a treatment algorithm for HS (see **Figure 2**).[5] Treatment should be based on disease severity, and should take account of inflammatory components of the disease as well as scarring.[5,42] Modalities should include surgery as well as pharmacological therapy.[5,42] All patients should be offered adjuvant therapy for pain, weight loss, tobacco cessation, treatment of super infections and application of appropriate dressings.[5,42]

The most common comorbidities and complications of HS are:

- Smoking
- Inappropriate diet
- Obesity
- Scarring
- Obstruction of lymph drainage
- Psychological impact.[46]

Metabolic disorders associated with HS can be addressed in primary care with appropriate intervention and referral.[24]

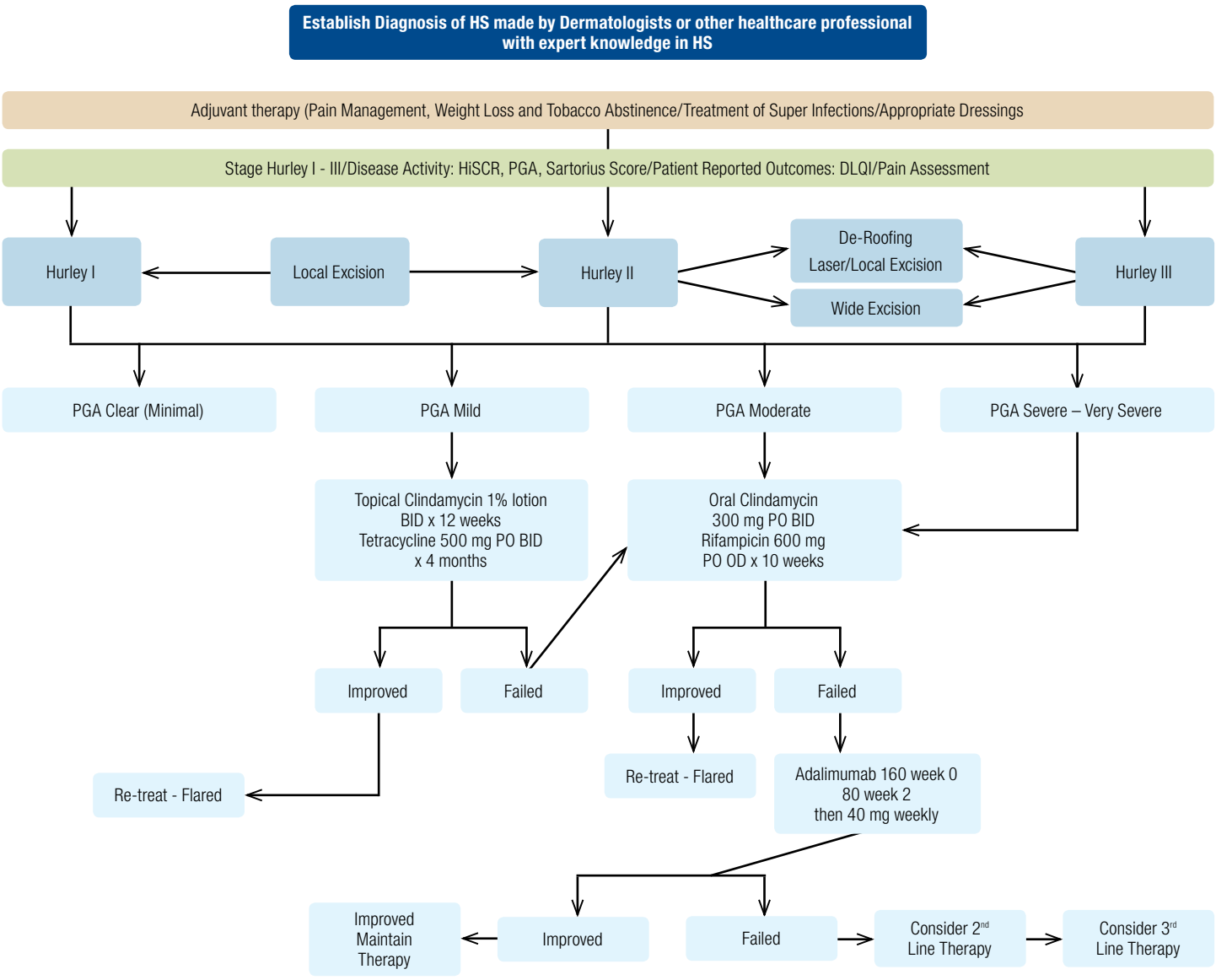

Figure 2. Treatment algorithm for HS (reproduced from Gulliver W, et al. Rev Endocr Metab Disord. 2016 Sep;17(3):343-351).[5]

Treatment of HS in the emergency department should be limited to management of acute deterioration of symptoms or side effects of management.[24,47] Patients seen in emergency departments are often treated with simple incision and drainage and a short course of antibiotics.[24,47] Other complications that may present acutely include cellulitis and sepsis, as well as complications from chronic inflammatory disease such as anaemia, hypoproteinaemia, reactive arthritis, ophthalmic complications such as keratitis and corneal ulcerations, and mental health crises.[24,47]

To ensure adherence with treatment, patients should be educated at the time of diagnosis about the complex nature of HS and its comorbidities.[34] Poor adherence to treatment leads to a larger component of disease-specific cost allotted to inpatient and emergency department care than other chronic skin conditions such as psoriasis.[48] Patients should be referred to support groups, and may also require specialist psychology and psychiatry services.[30,34]

Pharmacological treatment

First-line pharmacological therapies for HS include topical clindamycin, oral tetracycline, oral clindamycin/rifampicin and subcutaneous adalimumab, and these are discussed in more detail below.[5] Second-line therapies include zinc gluconate, resorcinol, intralesional corticosteroids, systemic corticosteroids, acitretin/etretinate and infliximab.[5] Third-line therapies include colchicine, botulinum toxin, isotretinoin, dapsone, cyclosporine and hormones.[5]

Topical clindamycin

Clindamycin 1% lotion is the only antibiotic that has been studied as a topical agent for the treatment of HS.[5,42] A randomised controlled trial in 27 patients with Hurley stage I or mild stage II HS found that clindamycin 1% lotion reduced superficial lesions such as folliculitis, papules and pustules.[49] Clindamycin is thought to exert its effects via a bacteriostatic action.[42] It is recommended as first-line therapy for patients with PGA mild HS or localised Hurley stage I/mild Hurley stage II HS, particularly when no deep inflammatory lesions are present.[5] If clinical response is not achieved after twice-daily treatment for 12 weeks, other options must be considered.[5]

Systemic antibiotics

Oral tetracycline 500 mg twice daily was as effective as topical clindamycin 1% in a randomised controlled trial of 46 patients with Hurley stage I or II HS.[50] The anti-inflammatory properties of tetracycline are likely to be responsible for its efficacy in this patient population.[51] Oral tetracycline 500 mg twice daily is recommended as first-line therapy for patients with PGA moderate HS or more widespread Hurley stage I/mild Hurley stage II HS, particularly when no deep inflammatory lesions are present.[5] If clinical response is not achieved after treatment for 4 months, other options must be considered.[5]

Three case series found that oral clindamycin 300 mg twice daily combined with oral rifampicin 600 mg once daily or 300 mg twice daily was effective in patients with HS.[52,53,54] The combination is thought to have immunomodulatory and anti-inflammatory effects in this patient population.[55] Clindamycin + rifampicin is recommended as first-line therapy for patients with PGA moderate to severe HS or Hurley stage II HS for a period of 10 weeks.[5] Other treatments must be considered if clinical responses are not achieved within this time.[5]

Adalimumab

The efficacy and tolerability of subcutaneous adalimumab 40 mg/week for the treatment of patients with moderate to severe HS has been demonstrated in randomised controlled trials involving a total of 787 patients.[8,43] A phase 2 dose-ranging trial[43] was followed by the phase 3 PIONEER I and II trial,[8] leading to regulatory approval of adalimumab for moderate to severe HS.[8] A long-term extension study showed that the benefit of adalimumab was maintained over a 3-year period, with no additional safety issues.[56] A recent analysis of data from PIONEER I and II has also confirmed the rapid effectiveness of adalimumab in alleviating skin pain.[57]

An updated summary of a 2016 Cochrane Review concluded that there is high-quality evidence of benefit with weekly adalimumab for patients with HS.[7] Adalimumab is recommended as first-line therapy for patients with moderate to severe HS who are unresponsive or intolerant to oral antibiotics.[5] To access adalimumab through the Pharmaceutical Benefits Scheme in Australia, it must be prescribed by a dermatologist.[9]

For adults, the initial dose of adalimumab should be 160 mg, given as two 80 mg injections in one day, one 80 mg injection for two consecutive days, four 40 mg injections in one day or two 40 mg injections for two consecutive days.[58] Two weeks later, adalimumab 80 mg should be given as either one 80 mg injection or two 40 mg injections.[58] At week 4, adalimumab should be continued at a dose of 40 mg per week.[58] For adolescents (from 12 years of age and weighing >30kg), the initial dose of adalimumab should be 80 mg, given as one 80 mg injection or two 40 mg injections, followed by 40 mg fortnightly, starting 1 week later.[58] An increase in dose frequency to 40 mg every week can be considered in adolescents with an inadequate response to fortnightly adalimumab.[58]

Adalimumab should be discontinued in patients showing no benefit after 12 weeks,[58] and second-line treatment options must be considered.[5]

PIONEER I and II trials[8]

Patients enrolled in PIONEER I (n = 307) and II (n = 326) had moderate to severe HS with a total abscess and inflammatory nodule count ≥3 at baseline, an inadequate response to oral antibiotics, and had not previously received anti-TNF-α treatment. Patients in PIONEER I stopped oral antibiotic treatment ≥28 days before study entry, while 19% of patients in PIONEER II continued to receive tetracycline at stable doses. Patients in PIONEER I had a higher mean bodyweight and a greater disease burden than those in PIONEER II. All patients used a daily antiseptic wash on their lesions.

Both PIONEER I and II were multicentre trials with two double-blind, placebo-controlled periods. In period 1, patients were randomly assigned in a 1:1 ratio to receive adalimumab 40 mg weekly or placebo for 12 weeks. In period 2, patients were reassigned to adalimumab 40 mg weekly or every other week, or placebo, for 24 weeks. The primary endpoint was the proportion of patients with a clinical response at week 12, defined according to the HiSCR measure as a >50% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count.

The proportion of patients with a clinical response at week 12 of period 1 was significantly higher in the adalimumab vs placebo groups: 41.8% vs 26.0% in PIONEER 1 (p=0.003) and 58.9% vs 27.6% in PIONEER II (p<0.001) (see **Figure 3a** and **Figure 3b**). In the PIONEER II trial, patients who received adalimumab had significantly greater improvement in rank-ordered secondary outcomes (p=0.01 for total abscess and inflammatory nodule count of 0-2 for patients with Hurley stage II disease at baseline, p<0.001 for 30% reduction in skin pain score vs baseline, and p<0.001 for mean improvement in the modified Sartorius score) at week 12 compared with placebo recipients.

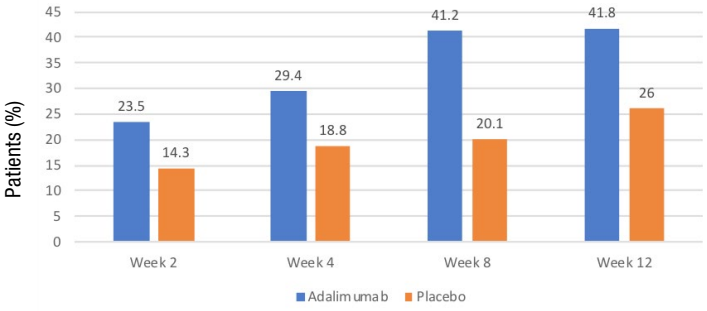

Figure 3a. Patients with clinical response according to HiSCR in period 1 of the PIONEER I trial.[8]

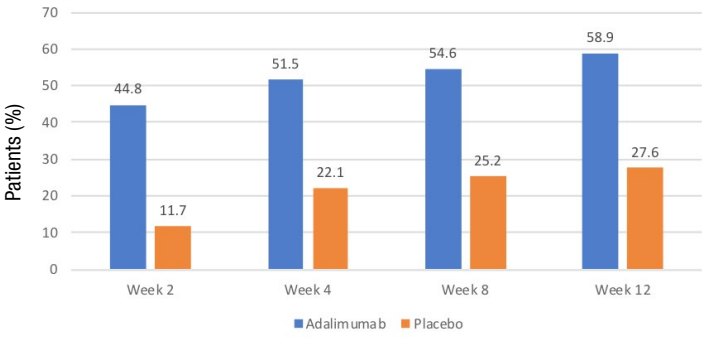

Figure 3b. Patients with clinical response according to HiSCR in period 1 of the PIONEER II trial.[8]

Serious adverse events in period 1 occurred in 1.3% of patients receiving adalimumab and 1.3% of patients receiving placebo in PIONEER I, and 1.8% and 3.7% of patients, respectively, in PIONEER II. Serious adverse events occurred in ≤4.6% of patients in all groups in both studies during period 2, with no significant between-group differences.

Infliximab

Infliximab 5 mg/kg intravenously has been evaluated in a randomised, double-blind, placebo-controlled trial of 33 patients with moderate to severe HS.[59] There was no statistically significant difference between the infliximab and placebo groups for the primary endpoint (>50% improvement in HS Severity Index score) after 8 weeks of therapy.[59] However, 27% of infliximab recipients had a 25-50% improvement in HS Severity Index score compared with only 5% of placebo recipients ($p<0.001$).[59] Dermatology Life Quality Index and Visual Analogue Scale pain scores were also improved with infliximab vs placebo.[59] An updated summary of a Cochrane Review concluded there is moderate-quality evidence of benefit with infliximab for patients with HS.[7]

Treatment with intravenous infliximab 5 mg/kg at week 0, 2, 6 and every 2 months thereafter for 12 weeks is recommended for patients with moderate to severe HS as a second-line option, after failure of adalimumab.[5] It should be noted, however, that infliximab does not have regulatory approval in Australia for the treatment of HS. Other treatments must be considered if clinical response is not achieved after 12 weeks.[5]

Surgery

Surgery is a common treatment modality for medically non-responsive HS lesions,[5,42] although there is no universal agreement about the stage at which surgical intervention should take place.[34] Evidence-based studies of surgical techniques are sparse, with most literature comprising case series and retrospective reports.[6,60] The type of surgery chosen depends on the body region and severity of disease.[42] Options include wide excision, local excision, deroofing, carbon dioxide laser therapy, Nd:YAG laser therapy and intense pulsed light.[5,42] In a meta-analysis of surgical techniques for HS, recurrence rates were 13% for wide excisions, 22% for local excisions and 27% for deroofing.[61]

Lasers and intense pulsed light

The use of lasers and intense pulsed light for the treatment of HS has increased over recent years.[62] Carbon dioxide laser is used for cutting or vaporisation of stationary disease elements,[62] however recurrence rates have varied across studies.[5] Nd:YAG laser and intense pulsed light destroy hair follicles and are thus able to reduce disease activity in the treated area.[62] A randomised controlled study of Nd:YAG laser in 22 patients with Hurley stage II-III HS found disease severity significantly improved after 3 one-monthly treatment sessions ($p<0.05$ vs baseline).[63] A significant improvement in mean examination score occurred in 18 patients with HS randomised to twice-weekly treatment with intense pulsed light for 4 weeks on one side of bilaterally affected region, and this was maintained at 12 months ($p<0.001$).[64]

Expert commentary – Associate Professor Saxon Smith

HS is a challenging condition to treat as no one treatment is the perfect fit for all patients. Antibiotics with inflammatory properties remain the first line of defence. These often need to be continued for extended periods of time. However, in the current environment of antibiotic stewardship, this needs to be carefully considered.

For patients with polycystic ovary syndrome, they may find longer term control from the use of spironolactone and/or metformin. This is especially the case in females whose HS seems to flare with their menstrual cycle. These can be long term agents in those in whom they help. However, there are many in whom these are not successful.

The main randomised control trials that have been completed in the management of HS have been with the TNF-α inhibitor adalimumab. It is available under the Pharmaceutical Benefits Scheme through a dermatologist for the treatment of significant disease which is not responsive to separate course of 2 different antibiotics taken for a minimum of 3 months. Patients must demonstrate a minimum 50% improvement in their abscess and nodule count after 12 weeks of therapy to continue on adalimumab therapy. Clinically, patients will see around a 70% reduction in the activity of their disease. The most striking positive impact from treatment is the pain relief that patients get from this treatment. Such that even if they do still have some disease activity their quality of life is significantly improved.

Further clinical trials exploring other biologic agents are underway around the world, and it is hopeful that there will be more options for medical therapy over time.

Surgical intervention also remains part of the multimodal treatment response for HS. Incision and drainage provides temporary relief but unfortunately the abscess and cysts often reform. Excision of individual lesions is possible but in the setting of significant active disease deroofing procedures are more easily performed and have a higher success rate. Carbon dioxide lasers are being used overseas as part ablative and part surgical procedure with positive results. There are times though that large complex surgeries can be performed, especially for localised axillary disease. This step is only taken after careful consideration and maximising disease control through pharmacological means preoperatively. However, there is a large operator-dependent factor with all of these interventions and it is important to understand that HS is an inflammatory condition rather than a typical infective abscess.

Conclusions

Potential future directions

Since development of the European guidelines and treatment algorithm for HS,[5,42] small studies evaluating an IL-1 antagonist, an IL-12/23 inhibitor and a PDE4 inhibitor for the treatment of HS have shown beneficial effects.[65,66,67] Several more studies of biological agents, including an IL-1α antagonist, IL-17 inhibitors, and a complement C5A inhibitor, are currently recruiting patients or are awaiting publication.[68] Future studies are needed to evaluate the effectiveness of combination treatment regimens in HS.[68]

Available support services

An Australian patient education website, HS Online (www.hs-online.com.au), is a useful resource which has been developed by both physicians and patients. A peer support group for Australian patients with HS can be found on Facebook (www.facebook.com/groups/hssufferersinaustralia/).

Expert conclusions – Associate Professor Smith

HS is a condition that once recognised can be more effectively managed and improve patient's quality of life. A high index of clinical suspicion is required. However, recurrent scarring abscesses and nodules in the axillae, inframammary, infra-abdominal apron, groin and buttock area is a consistent clinical sign which should help guide clinicians to consider the diagnosis. The presence of double headed comedones is almost pathognomic and should be looked for to help confirm the diagnosis. Furthermore, where possible, a referral to a dermatologist can help confirm the diagnosis but more importantly start the patient on the right journey to better management of their condition.

Expert conclusions – Professor Braitberg

Engagement of primary care practitioners is essential in ensuring the early diagnosis of HS. It is also necessary in allowing effective management of comorbidities and lifestyle issues, and in providing high quality care coordination to mitigate the impact and manage the outcome of complications of care.

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