
In this issue, we discuss a recent update to the British Association of Dermatologists management of HS guidelines as well as graded evidence-based treatment optimisation recommendations from the International HS ALLIANCE working group. Also featured in this review are findings from 3 large-scale population-based studies that show an increased prevalence, and a strong independent association, between psoriasis and HS, acne vulgaris and HS and psychiatric disorders with HS. We finish this issue with a retrospective analysis of a real-world Greek cohort that showed a significant mean annual cost reduction in the treatment of patients classified with Hurley Stage III HS by adalimumab treatment compared to non-anti-tumour necrosis factor therapies.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,
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British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018

Authors: Ingram JR et al.

Summary/Comment: The British Association of Dermatologists have released their guidelines for the management of hidradenitis suppurativa (HS). Like all guidelines, they are often produced based around the specific clinical and health economic demands within the country they pertain too. However, they do help to provide broad evidence and support for the treatment of this complex inflammatory dermatosis. There are several key messages worth highlighting. One of the interesting parts of their treatment algorithm is that they have recommended rifampicin and clindamycin in combination as their second line after the failure of a trial of monotherapy with a tetracycline. Whilst this would fit within the framework with Australia, especially in the moderate to severe patients, it would be more common practice to trial an alternative tetracycline with mild to moderate patients before escalating to the antibiotic combination. But perhaps the significant departure in terms of applicability to Australia, is that should a patient fail to respond to rifampicin plus clindamycin in combination as their second line after the failure of a trial of monotherapy with a tetracycline. Whilst this would fit within the framework with Australia, especially in the moderate to severe patients, it would be more common practice to trial an alternative tetracycline with mild to moderate patients before escalating to the antibiotic combination. But perhaps the significant departure in terms of applicability to Australia, is that should a patient fail to respond to rifampicin plus clindamycin in combination, these guidelines suggest trialling dapson or actretin before adalimumab. Whilst these agents are relatively inexpensive, they have significantly lower evidence of efficacy than adalimumab as well as significant side effect profiles. They do highlight the potential role of infliximab in patients who are failing to respond to adalimumab. Ultimately guidelines now tend to be living documents allowing them to be updated more regularly with advancements. This will especially be the case with the weight of research and pharmaceutical trials happening in Australia and around the world.


Abstract

Abbreviations used in this issue:

AV = acne vulgaris; CI = confidence interval; HiSCR = Hidradenitis Suppurativa Clinical Response; HS = hidradenitis suppurativa; IL = interleukin; MH = mental health; MSC = mesenchymal stem cell; OR = odds ratio; TNF = tumor necrosis factor.

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Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization – systematic review and recommendations from the HS ALLIANCE working group

Authors: Zouboulis CC et al.

Summary: The HS ALLIANCE working group, an International group of dermatology experts representing 25 different countries, performed a systematic literature review to answer 9 overarching key clinical questions and graded the evidence to provide clinical recommendations for the treatment and management of patients with HS. The recommendations cover topics such as comorbid disease identification, therapy with antibiotics and biologics or surgical intervention and monitoring. A search of PubMed/Medline, The Cochrane Library, EMBASE, CINAHL, SCOPUS, BIOSIS and Web of Science yielded 5310 articles. After screening and analysing, 65 articles comprised of randomised controlled trials, prospective and retrospective studies and case series with ≥10 cases, published between August 1996 and August 2016 were included as evidence for the formation of the final recommendations. The Oxford Centre for Evidence-based Medicine criteria was used to grade evidence. The main recommendations are as follows:

1. Comorbidities including smoking, cardiovascular disease, metabolic syndrome, obesity, depression and diabetes mellitus should be considered

2. Treatment recommendations were divided into medical therapies including:
   i) non-biologic therapies – clindamycin and rifampicin (300 mg twice daily for 10-weeks)
   ii) antibiotics – topical clindamycin 1%, systemic tetracyclines, triple regimen of rifampicin (10 mg/kg once daily), moxifloxacin (400mg once daily) and metronidazole (500 mg thrice daily) for up to 12-weeks, 6-week course of etretinate. They also noted that microbiological cultures are not useful
   iii) biologics – Adalimumab first choice after failure of conventional treatment, 2nd line infliximab, 3rd line anakinra. Etanercept is not effective for the treatment of HS.
   iv) combination therapy - oral zinc glucinate (30 mg thrice daily) and topical triclosan 2% (twice daily), intralesional steroids, low-dose systemic corticosteroids (10 mg prednisolone equivalent)

Or surgical treatment – limited excision for solitary lesions. Wide excision of entire affected areas in some circumstances.

3. Monitoring – assessment of baseline severity should be measured by Hurley stage measurement. HS clinical response and patient-reported outcomes measures are useful tools.

The group also noted that very little high-quality evidence is available and research into optimal treatment regimens for long-term cardiovascular outcomes should be a priority.

Comment: The European HS Alliance working group have also updated their HS management. Many of us will recall their original management guidelines from several years ago. Like the British Association of Dermatologists guidelines, the European management recommendations help highlight the gradual shift in evidence in the treatment of HS. The general current level of evidence for many treatments are low and probably directly reflect the variability of their success in the clinical situation. As stated above, dapsona has and can be trialled, however this is based on a solitary level 4 trial. The HS Alliance have examined an alternative antibiotic combination in lieu of rifampicin and clindamycin. They have suggested a triple therapy combination of rifampicin + moxifloxacin + metronidazole. This is based on level 4 evidence from a single trial. In the new world of antibiotic stewardship and growing evidence of the inflammatory cytokine pathway as opposed to antibiotic pathway, new agents will likely bring a shift away from complex combinations of antibiotics except in rescue situations. In the meantime, it is good to have an alternative option up our sleeve for those treatment resistant patients.


Abstract

The anti-inflammatory potency of biologics targeting TNF-α, IL-17A, IL-12/23 and CD20 in hidradenitis suppurativa

Authors: Vossen ARJV et al.

Summary: This ex vivo study out of The Netherlands utilised lesional HS skin culture systems to investigate the specific inhibitory effect of a range of biologics, and the glucocorticoid prednisolone, on cytokines and antimicrobial peptides. Using real-time quantitative polymerase chain reactions and cytokine bead arrays, the investigators looked at both the mRNA expression and protein production changes in 10 skin lines from HS lesions and 5 healthy control lines. Biologics investigated included the tumor necrosis factor-α (TNF-α) inhibitors adalimumab and infliximab, interleukin (IL)-17A-inhibitor secukinumab, IL-12/23p40-inhibitor ustekinumab and rituximab. All anti-inflammatory agents tested significantly downregulated mRNA expression of all tested cytokines (p<0.0001). Adalimumab, infliximab, ustekinumab, prednisolone (all p<0.0001) and rituximab (p=0.0071) also inhibited protein production of the cytokines TNF-α, IFN-γ, IL-17, IL-6, and IL-17A, however, secukinumab did not (p=0.0663). In healthy control skin, a significant inhibitory effect on the mRNA expression of inflammatory markers was only observed for prednisolone (p=0.0015), adalimumab and infliximab (p<0.0001). The authors concluded that in HS lesional skin the most potent inhibitors of cytokines are prednisolone and TNF-α inhibitors such as adalimumab and infliximab.

Comment: A better understanding of the pathophysiology of HS will ultimately lead to a better approach to therapy. It is increasingly clear that HS is an inflammatory dermatosis with a signature of cytokines. The pro-inflammatory cytokines TNF-α, IFN-γ, IL-18, IL-6 and IL-17A have already been shown to play a central part in HS. IL-23 is being investigated with several clinical trials underway with IL-23 agents in HS but was not examined in this article. Vossen et al. examined lesional skin to see the impact on the cytokine disease signature of HS. Specifically, they looked at the relative mRNA expression of these cytokines. By decreasing mRNA expression, you have an inhibitory effect of the production of that specific cytokine. It is both surprising and not surprising that they demonstrated that prednisolone had a strong effect. However, it only remains a rescue remedy due to the medium and long term side effects. Their study does provide a pathophysiological strong evidence of the role of adalimumab and infliximab in HS.


Abstract

Independent Commentary by Clinical Associate Professor Saxon D Smith

Clinical Associate Professor Saxon D Smith is a consultant dermatologist in private practice in Gosford, Australia, a staff specialist at Royal North Shore Hospital, St Leonards, Australia and a clinical associate professor at the University of Sydney, Australia. He runs public clinics at Royal North Shore Hospital in surgical cutaneous oncology; immune-oncology management and surveillance in advance melanoma; multi-disciplinary team with plastic surgery on the management of hidradenitis suppurativa; multi-disciplinary team with neurology on skin diseases in neurology including management of adverse reactions of treatment; and dermatology in renal transplant patients.
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**References:**
**Pathogenetic characteristics of mesenchymal stem cells in hidradenitis suppurativa**

Authors: Campanati A et al.

**Summary:** This Italian prospective case-control study compared the immunophenotypic profile of mesenchymal stem cells (MSCs) from biopsies of HS patients and healthy controls to investigate the pathogenic involvement of MSCs in HS. Axillary skin punch biopsy samples were obtained from 11 patients with HS (8 women; mean age 35.6 years) and 9 healthy controls (7 women; mean age 37.6 years) seen at the Dermatological Clinic, Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy, between January 20, 2015 and September 20, 2016. HS patients were matched with healthy controls for body mass index. The secretome of isolated MSCs was analysed by enzyme-linked immunosorbent assay for levels of 12 cytokines involved in the helper-T cell 1, 2 and 17 pathways. HS-MSCs showed statistically significant overexpression of pro-inflammatory cytokines IL-6, IL-10, IL-12, IL-17A, TNF, transforming growth factor β1 and interferon γ (P=0.008, P=0.004, P=0.03, P=0.008, P=0.004, P=0.004 and P=0.005, respectively), compared to healthy MSCs. The authors hypothesised that MSCs play a pathogenic role in HS.

**Comment:** Understanding the evolving cytokine signature of HS is important for being able to gradually adopt a 'treat to target' approach to the management of HS. Furthermore, understanding the downstream effects of these cytokines in HS will help us better understand how our treatments are working and perhaps build a platform for future treatment modalities. This current study highlights that HS patients have a predisposition in their affected skin cells to be activated toward an inflammatory status when compared to normal patients. This is like a primed system that needs less of a push to get a larger inflammatory response to occur. It helps to understand the variation in response to therapy with some patients responding well whilst others less well. This is reflected in the clinical experience when using adalimumab, some patients have a dramatic improvement whilst others more a slower steady improvement. But the stand out feature with both tends to be the pain relief. On the other hand, it does not directly explain the hormonal component that many women suffer from especially with the strong relationship with polycystic ovarian syndrome. Perhaps it links to potentiating the pro-inflammatory state that abdominal adipose tissue has been shown to have. More questions to be answered as we peel away the onion layers of this complex disease.

**Reference:** JAMA Dermatol 2018;154(10):1184-90

**Psoriasis and hidradenitis suppurativa**

Authors: Kridin K et al.

**Summary:** This retrospective large-scale population-based study utilised a real-life Israeli database to investigate associations between psoriasis and HS. Patients (n=68,836) and control subjects (n=68,836) were matched for age, sex and ethnicity. The psoriasis group had a higher prevalence of HS than the control group (0.3% vs 0.2%, respectively; odds ratio [OR] 1.8; 95% confidence interval [CI], 1.5-2.3; P<0.001). Psoriasis was associated with HS in multivariate analysis adjusted for smoking, obesity and other comorbidities (OR, 1.8; 95% CI, 1.4-2.2; P<0.001). Compared to patients with psoriasis alone, those with co-existent psoriasis and HS were significantly younger (39 vs 42 years, P=0.015), had an increased prevalence of obesity (35.1% vs 25.3%, P=0.001) and smoking (58.5% vs 37.3%, P<0.001).

**Comment:** As we are starting to develop a clear picture of the inflammatory signature of HS, it is not surprising that we can identify a positive association with psoriasis and HS. TNF-α, IL-6, IL-17, IL-23 have been shown to have a clear signature of activity in psoriasis. As discussed in previous sections of this Research Review, these same cytokines play a central role in HS. Being able to start to see a clinical confirmation of this basic science picture is reassuring that our understanding of the disease is growing. Furthermore, it opens the conversation for potential other treatment options targeting these cytokines in patients with a disease that has been too long put in the ‘too hard basket’.


**Overall and subgroup prevalence of acne vulgaris among patients with hidradenitis suppurativa**

Authors: Wertenteil S et al.

**Summary:** This US cross-sectional study analysed electronic health records from a population-based sample of over 55 million adults to ascertain the prevalence of acne vulgaris (AV) in patients with HS. Compared to adults without HS, adults with HS had a statistically significant increased prevalence of AV (2.9% vs 15.2%, respectively; P<0.001) and 4.51 times the odds of having AV (95% CI, 4.40-4.63). Amongst HS patients, the highest prevalence of AV was seen in patients who had polymyxin ovary syndrome (28.7%), aged 18-44-years (18.2%), non-white (17.5%), female (16.4%) or obese (15.5%). The strength of the association between HS disease severity and AV was not assessed.

**Comment:** Traditionally HS was part of the ‘follicular occlusion’ tetrad of HS, severe acne or acne conglobata, pilonidal sinus and dissecting cellulitis of the scalp. It is important to look at this tetrad through the prism of our increasing understanding of this condition. Interestingly, in discussion with some surgeons who understand HS, it is becoming apparent that when looking at pilonidal sinus it probably sits on a spectrum with HS. For example, at time of resection, some pilonidal sinuses are full of curled hairs as expected from the traditional explanation of the formation of a pilonidal sinus. Whereas others demonstrate none of these hairs but more typical HS inflammation.

However, Wertentiel et al could not find a strength of association between HS and acne vulgaris severity. Perhaps an underlying issue with this is the high frequency of acne vulgaris versus the much lower frequency of HS. It will be interesting to see if there are further reviews examining this historical association further.


**Adolescent-onset hidradenitis suppurativa: prevalence, risk factors and disease features**

Authors: Molina-Leyva A et al.

**Summary:** This Spanish cross-sectional study investigated the prevalence of, and risk factors for adolescent-onset HS. 134 patients with HS seen at Hidradenitis Suppurativa Clinic, Dermatology Department, Hospital Universitario Virgen de las Nieves, Granada, Spain, were included in the analysis. 51.5% of patients had HS onset present during adolescence. A higher risk of early onset was seen in female patients, those with a family history or presence of pilonidal sinus or acne conglobata. Patients with adolescent-onset HS experienced longer disease duration.

**Comment:** It is not uncommon for patients to describe that their symptoms for HS started when they were young. Often it is mild and intermittent in nature. However, the disease can significantly escalate in their late teens and early twenties. Coupled with this, HS is a disease of progression where it is believed it will worsen over time around the intermittent flares. Overtime the flares can become more frequent and ultimately constant for some patients. Therefore, if we are able to identify and manage HS patients in the early years of their disease it may circumvent this risk of progression and all the impacts the disease can have both physiologically and psychologically.

**Reference:** Dermatology 2019;235(1):45-50

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Association between hidradenitis suppurativa and hospitalization for psychiatric disorders

Authors: Patel KK et al.

Summary: This cross-sectional analysis of the 2002-2012 national Inpatient Sample (n=87,053,155 hospitalisations ~ 20% of all US hospitalisations) investigated mental health (MH) comorbidities of HS and the associated cost burden. Compared to patients without HS, those with HS had a higher prevalence of MH disorders (20.05% vs 34.22%, respectively) and significantly higher odds of a comorbid MH disorder (adjusted OR 2.53). The excess annual cost of hospitalisations for MH disorders in HS patients was calculated to be >$38 million.

Comment: There is a clear association with chronic illnesses with the development of depression. HS is disease associated with painful unpredictable flares, odorous discharge and scarring. Therefore, it is not surprising that HS has an association with depression and anxiety. This was again confirmed by Patel et al. in their article. This adds to both the potential health burden on the individual patient as well as additional health costs more broadly. Therefore, it is important to acknowledge and address potential mental health issues in this population.


To what extent do disease severity and illness perceptions explain depression, anxiety and quality of life in hidradenitis suppurativa?

Authors: Pavon Bianco A et al.

Summary: This UK cross-sectional study investigated the impact of HS severity on mental health and quality of life. The clinician-assessed Hurley Staging System was used to stratify HS severity on mental health and quality of life. The clinician-assessed disease severity. Patients with HS which was compared to patient-reported questionnaires – the Brief Illness Perception Questionnaire, the Patient’s Health Questionnaire-2, the Generalized Anxiety Disorder-2 and the Dermatology Life Quality Index. Patient-perceived illness severity strongly associated with levels of depression, anxiety and quality of life, far more strongly than clinician-assessed disease severity.

Comment: Blanco et al have further explored this relationship between mental health and HS. When a patient suffers a chronic disease the feeling of low personal control over their illness and in turn over their lives is a key driver in the mental health and HS relationship. Patients will make small incremental changes to their life and lifestyle to compensate for their disease. Sometimes these are obvious, such as being limited by pain during flares. Other times these changes are smaller adjustments such as wearing darker coloured clothes to better hide the wetness from the discharging abscesses and sinuses. All of these are additive to the overall impact of HS on a patient’s activities of daily living.


Cost-savings of adalimumab in hidradenitis suppurativa

Authors: Argyropoulou M et al.

Summary: This retrospective analysis of a real-world cohort, carried out by Argyropoulo et al, from 4th Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece, investigated the financial efficacy of anti-TNF agent treatment of HS. 250 patients with Hurley Stage II and III HS, who had 1211 visits between September 2003 and December 2016, were included in the analysis. All costs were calculated based on the cost of items provided in current price lists. Containment of exacerbations was used to define effectiveness of treatment. The primary outcome measure was cost savings of anti-TNF therapy compared to all other treatment regimens. Treatment with anti-TNF agents resulted in exacerbation containment in a higher percent of cases than other therapies (63.4% vs 25.1%, respectively) and saved €178.92 per patient visit. 2-way analysis of variance showed that anti-TNF treatment was an independent variable affecting annual cost. The mean annual cost for Hurley Stage III HS was significantly reduced from €8309.60 using other therapies to €3264.20 with anti-TNF treatment (P=0.004).

Comment: Adalimumab remains the only disease modifying drug listed on the PBS in our armoury for HS. In the European guidelines above, they have made the step to state that adalimumab should be considered first line in moderate to severe patients. However, the cost of the medication means that, in Australia, it is limited to a patient population who have failed to respond to 2 different antibiotic courses for a minimum of 12-weeks each. There is an evidence base that infliximab may be considered as second line to adalimumab (level 2). However, it is not PBS listed for this purpose in Australia. Furthermore, infliximab has a high cost associated with it. Therefore, Argyropoulou et al have attempted to explore the cost-benefit of using anti-TNF. The current falling Australian dollar makes it difficult to translate the $ into AUD$. Their findings do indicate a cost benefit despite the high drug cost.


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