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GUIDELINES

European S2k guidelines for hidradenitis suppurativa/acne inversa part 2: Treatment

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Abstract

Introduction: This second part of the S2k guidelines is an update of the 2015 S1 European guidelines.

Objective: These guidelines aim to provide an accepted decision aid for the selection, implementation and assessment of appropriate and sufficient therapy for patients with hidradenitis suppurativa/acne inversa (HS).

Methods: The chapters have been selected after a Delphi procedure among the experts/authors. Certain passages have been adopted without changes from the previous version. Potential treatment complications are not included, being beyond the scope of these guidelines.

Results: Since the S1 guidelines publication, validation of new therapeutic approaches has almost completely overhauled the knowledge in the field of HS treatment. Inflammatory nodules/abscesses/draining tunnels are the primary lesions, which enable the classification of the disease severity by new validated tools. In relation to the degree of detectable inflammation, HS is classified into the inflammatory and the predominantly non-inflammatory forms. While the intensity of the inflammatory form can be subdivided by the IHS4 classification in mild, moderate and severe HS and is treated by medication accordingly, the decision on surgical treatment of the predominantly non-inflammatory form is based on the Hurley stage of the affected localization. The effectiveness of oral tetracyclines as an alternative to the oral combination of clindamycin/rifampicin should be noted. The duration of systemic antibiotic therapy can be shortened by a 5-day intravenous clindamycin treatment. Adalimumab, secukinumab and bimekizumab subcutaneous administration has been approved by the EMA for the treatment of moderate-to-severe HS. Various

For affiliations refer to page 33.

surgical procedures are available for the predominantly non-inflammatory form of the disease. The combination of a medical therapy to reduce inflammation with a surgical procedure to remove irreversible tissue damage is currently considered a holistic therapeutic approach.
Conclusions: Suitable therapeutic options while considering HS severity in the therapeutic algorithm according to standardized criteria are aimed at ensuring a proper therapy.

OBJECTIVES OF THE GUIDELINES

The present second part of the S2k guidelines is an update of the latest edition of the S1 European guidelines from 2015 and their algorithm.[1,2] The first part is parallelly published in the Journal of the European Academy of Dermatology and Venereology.[3] The chapters have been selected after a Delphi procedure among the experts/authors. Certain passages have been adopted without changes from the previous version. The general aim of these guidelines is to provide dermatologists in offices and clinics as well as physicians of other specialties with an accepted decision aid for the selection and implementation of appropriate and sufficient therapy of patients with hidradenitis suppurativa/acne inversa (HS). No comprehensive list of potential treatment complications is included, since this would be beyond the scope of these guidelines.

Improvement of the care of patients by implementation of guideline recommendations and optimization of the knowledge of physicians with respect to effectiveness proven in studies

Personal experience and traditional therapeutic concepts of physicians concerning the efficacy of individual therapies of HS shall be complemented and, if necessary, replaced by the consented recommendations.

Aid for stage-related implementation of therapies according to the predominant severity

Especially, the presentation of suitable therapeutic options while considering the severity of HS in the therapeutic algorithm is aimed at ensuring a correct therapy.

Reduction in severe disease courses and scar formation

The comprehensive presentation of systemic therapies with detailed description of their use has the aim to overcome reservations concerning these therapeutic procedures among physicians and patients and to ensure their timely, sufficient and optimal implementation. The timely initiation of sufficient therapies is aimed at reducing severe disease courses that are often accompanied by pronounced scarring. This includes the development of therapeutic objectives and targets used to monitor treatment success and to change the therapy, if necessary.

Key points

Why was the study undertaken?

- Since the S1 guidelines publication in 2015, validation of new therapeutic approaches has almost completely overhauled the knowledge in the field of hidradenitis suppurativa treatment.

What does this study add?

- New hidradenitis suppurativa classification: inflammatory form (mild, moderate and severe; IHS4 classification) and predominantly non-inflammatory form (Hurley staging). Algorithm of predominantly medical (oral tetracyclines vs. clindamycin/rifampicin, short-term intravenous clindamycin, EMA-approved biologics: adalimumab, secukinumab and bimekizumab) and surgical treatment (various procedures), respectively.

What are the implications of this study for disease understanding and/or clinical care?

- A therapeutic algorithm with suitable therapeutic options while considering HS severity according to standardized criteria ensure a proper therapy. The combination of medical therapy reducing inflammation with surgery to remove irreversible tissue damage is considered a holistic therapeutic approach.

Promotion of compliance

Compliance is often associated with a ratio of benefit to effort, costs and adverse effects acceptable for the patient. The

individual selection of particularly effective therapies, taking also the parameters on quality of life assessed in new studies into account, has the aim to ensure an especially high therapeutic benefit for the patients. Information about treatment and avoidance of adverse effects is aimed at avoiding or reducing these effects, thus further promoting compliance.

OBJECTIVES OF HS TREATMENT

Regular control and, if necessary, adjustment of the therapy with respect to potentially changing disease severity are advisable. This is also required to ensure compliance (timely modification of therapy in patients responding inadequately to therapy or in case of adverse drug reactions). The assessment should be performed according to standardized criteria[4] taking the objectifiable lesions into account and after recording the disease-related impairment of the quality of life of the patient. If no significant reduction in the inflammatory activity of the lesions or no improvement of the quality of life is observed after 12 weeks, the therapy should be modified while taking the partly different rates of effectiveness into account. The recommended indicators for assessment are depicted in the first part of the guidelines under 'Severity classification and assessment'.

WHAT'S NEW?

Since the publication of the S1 guidelines in 2015,[1] validation of new therapeutic approaches has almost completely overhauled the knowledge in the field of HS treatment. Inflammatory nodules and abscesses (AN), and draining tunnels are the primary lesions of the disease, which enable the calculation of the disease severity by new validated classification tools, especially the International Hidradenitis Suppurativa Severity Scoring System (IHS4).[4] HS is classified into two forms in relation to the degree of detectable inflammation: the inflammatory and the predominantly non-inflammatory form.[5,6] While the intensity of the inflammatory form can be subdivided by means of the IHS4 classification in mild, moderate and severe HS and is treated by medication accordingly, the decision on surgical treatment of the predominantly non-inflammatory form is based on the Hurley stage of the affected localizations, that is Hurley stage I, II and III.[5,7] Concerning the field of classical drug therapy, the effectiveness of systemic oral tetracyclines, which is similar to the effectiveness of oral systemic combination of clindamycin and rifampicin, should be noted.[8] In addition, it may be possible to shorten the total duration of systemic antibiotic therapy to a 5-day systemic intravenous (i.v.) therapy of clindamycin.[9] On the contrary, the number of clinical trials with biologics is constantly increasing. Adalimumab,[10] secukinumab[11] and bimekizumab[12] have been approved as subcutaneous (s.c.) injections for the therapy of HS. Various surgical procedures are available for the predominantly non-inflammatory form of the disease. The combination of a medical therapy to reduce inflammation with a surgical procedure to remove irreversible tissue damage is currently considered a holistic therapeutic approach in HS.[13]

SCORING SYSTEMS FOR HS CLINICAL TRIALS

For a chronic, recurrent, inflammatory disease like HS, it is important to have a scoring system that is well validated and can serve as primary outcome for clinical trials. Important key points for such a score are validation against other physician and patient-reported outcomes, ability to be used both in clinical trials and daily clinical practice, validation in different datasets, be dynamic, consensus-based and provide an acceptable intra- and interobserver variability (Table 1).[14]

Hidradenitis suppurativa clinical response (HiSCR)

The HiSCR was developed retrospectively from a phase 2 randomized controlled trial involving adalimumab treatment, which used other outcome measures in the trial itself.[15] The HiSCR identifies responders as those who achieve at least a 50% reduction in AN count without an increase in the number of abscesses or draining tunnels relative to baseline. Later on, in the pooling dataset of phase 3 adalimumab trails, HiSCR has been validated and it has been shown that irrespective of treatment, significantly more HiSCR responders than non-responders experienced clinically meaningful improvement in Dermatology Life Quality Index (DLQI), Pain Numeric Rating Scale (NRS), Hidradenitis Suppurativa Quality of Life (HS-QoL), work-related performance and non-work-related performance.[16]

Although it has been adopted as Federal Drug Administration (FDA)-supported primary endpoint in almost all randomized controlled trials (RCT) subsequently, the drawbacks of HiSCR have become increasingly apparent in recent clinical trials. Firstly, patients with an AN count <3 were excluded from the clinical trial in which the HiSCR was developed. This means that HiSCR may be less stable in patients with an AN count <3 and it is, therefore generally not used in such patients. Consequently, these patients are excluded from participating in all clinical trials that use HiSCR as the primary endpoint. Secondly, the HiSCR does not dynamically take into account draining tunnels.

TABLE 1 Scoring systems for clinical trials of HS and their grade of recommendation.

Recommendation		HS scoring system
↑↑	Should be recommended	IHS4 IHS4-55
↑	Could be recommended	HiSCR HS-IGA
↔	May be considered	HASI-R SAHS

During recent clinical trials, other drawbacks of the HiSCR were identified. In particular, the SHINE study, a phase 2 RCT assessing the efficacy of vilobelumab/IFX-1 in patients with moderate-to-severe HS compared with placebo was instrumental in bringing these drawbacks to light.[17] In this trial, the HiSCR rate was not statistically different between active treatment and placebo group, even though patients in the highest dosed treatment group achieved a significantly greater reduction in AN count and draining tunnels relative to the placebo group at Week 16. This highlights the drawback that HiSCR, by not dynamically incorporating draining tunnels, cannot fully capture the effect of anti-inflammatory treatment.

IHS4 and IHS4-55

IHS4 is a validated tool to dynamically assess HS severity and can be used both in real-life and in the clinical trials setting. IHS4 is calculated by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of ≤3 or less signifies mild, 4–10 signifies moderate and ≥11 signifies severe disease. It correlates well with Hurley classification, Expert Opinion, Physician's Global Assessment, Modified Sartorius score and DLQI.[4] It has been used as an entry criterion for inclusion in clinical trials and has been suggested as a paediatric clinical trial inclusion criterion.[18] Inter-rater and intra-rater agreement was found to be good and intra-rater reliability was very good.[19,20] The continuous IHS4 score has been adopted as a secondary outcome measure, in addition to the HiSCR, in many recently completed, ongoing and upcoming clinical trials. However, the preference of the FDA for a dichotomous outcome has resulted in the continuous IHS4 not being implemented as a primary outcome even after the drawbacks of the HiSCR have been highlighted.

Therefore, IHS4-55,[21] a dichotomous version of the IHS4, has been developed and validated both in phase 3 clinical trials setting for biologic agents and in datasets with patients treated with antibiotics.[8] The optimal cut-off threshold was identified as a 55% reduction in total IHS4 score. The performance of the IHS4-55 was presented to be similar to that of HiSCR in the PIONEER datasets while addressing the main drawbacks of the HiSCR.[21] The dichotomous IHS4 takes draining tunnels into account in a dynamic and validated manner, and it does not exclude patients with an AN count <3 but many draining tunnels. The best performing cut-off for the IHS4 was a 55% reduction in the IHS4 score (IHS4-55). Patients who achieved the IHS4-55 had an odd's ratio of 2.00 (95%-CI 1.26–3.18, $p = 0.003$), 2.79 (95%-CI 1.76–4.43, $p < 0.001$) and 2.16 (95%-CI 1.43–3.29, $p < 0.001$) for being treated with adalimumab rather than placebo in PIONEER-I, PIONEER-II and the combined dataset, respectively. Additionally, achievement of the IHS4-55 was associated with a significant reduction in inflammatory AN and draining tunnels in all analysed datasets.

Moreover, the external validation of the dichotomous IHS4 in a large Europe-wide prospective antibiotics study showed that the score was not only responsive in patients treated with adalimumab but also in patients treated with secukinumab and antibiotics.[8,22] Achievers of the IHS4-55 demonstrated a significant reduction in the count of inflammatory AN and draining tunnels (all $p < 0.001$). Additionally, IHS4-55 achievers had an odds ratio (OR) for achieving the minimal clinically important change (MCIC) of DLQI, NRS pain and NRS pruritus of 2.16 (95% CI 1.28–3.65, $p < 0.01$), 1.79 (95% CI 1.10–2.91, $p < 0.05$) and 1.95 (95% CI 1.18–3.22, $p < 0.01$), respectively.

This evidence suggests that IHS4-55 is a well-validated outcome that can be used as a novel primary outcome for clinical trials and daily clinical practice and that IHS4-55 addresses some of the HiSCR drawbacks dynamically, by including draining tunnels in a validated manner. By allowing the analysis of patients with an AN count <3 but many draining tunnels, this outcome measure will improve inclusivity in clinical trials.

Severity Assessment of Hidradenitis Suppurativa (SAHS)

SAHS is a severity score, including number of involved regions (axillas, submammary areas, intermammary or chest, abdominal, mons pubis, groins, genital, perianal or perineal, gluteal regions and others [e.g. neck and retroauricular]), number of inflammatory and/or painful lesions other than tunnels and number of tunnels. It has been validated only in correlation with modified Sartorius and Hurley score and has been found well correlating with them.[23] Responsiveness to treatment has been tested in a prospective manner in a case series of treated patients from a single centre. A dichotomous outcome has not been developed yet. The validation in clinical trial settings and other datasets is also lacking.

Hidradenitis Suppurativa area and severity index revised (HASI-R)

HASI-R measures inflammatory colour change, inflammatory induration, open skin surface and extent of tunnels, in various body sites using an estimation of involved body surface area (BSA).[24] Each of these variables is scored on a Likert scale from 0 to 3 (0 = none; 1 = limited/mild, 2 = moderate, 3 = severe/extensive) based on the average intensity for each body site.

It has been shown that it has moderate inter-rater reliability and excellent intra-rater reliability.[24] Divergent validity, assessed by correlation with the reverse-scored DLQI, showed a weak, non-significant correlation. It has no established and validated cut-off points for severity group and has not been validated according to patient-reported outcomes. A dichotomous outcome has not been established and the validation in clinical trial settings and other datasets is

lacking. It remains unknown how the HASI-R performs in a diverse patient population and how responsive this score is to change after anti-inflammatory therapy.

HS-investigator global assessment (IGA)

The HISTORIC effort developed and provided initial validation for HS-IGA, an investigator global assessment HS-specific tool.[25] Regardless of lesion type, axillary and inguinal regions most influenced the HS-IGA score. The score was well correlated with HS-physician global assessment (PGA) and HiSCR along with DLQI, NDS pain and HS-QoL .

Use of scoring systems that evaluate draining tunnels in a validated manner (Table 1)			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	34/34 (100%)

OVERVIEW OF THERAPEUTIC OPTIONS

Currently, the tumour necrosis factor (TNF)-α inhibitor adalimumab, the interleukin (IL)-17A inhibitor secukinumab and the IL-17A/F inhibitor bimekizumab are the only European Medicines Agency (EMA)-approved compounds for the medical treatment of HS.[26] Adalimumab is approved for the treatment of moderate-to-severe active HS in patients aged 12 years and older with inadequate response to conventional systemic HS therapy.[10,27] Secukinumab[11] and bimekizumab[12] are approved for the treatment of adult patients with moderate-to-severe active HS and inadequate response to conventional systemic HS therapy. All other therapeutic options discussed in this guideline—except for monotherapy with antibiotics—should be considered off label.

ADJUVANT THERAPY

General measures

General adjuvant measures in HS include weight loss, smoking cessation, physical exercise, healthy lifestyle, pain control (detailed information is provided in the section 'Lifestyle interventions, analgesics and wound care').

Local antiseptics

There is no scientific evidence to recommend the use of over-the-counter skin cleansers with antibacterial or anti-inflammatory properties such as chlorhexidine, benzoyl peroxide, zinc pyrithione, triclosan.[1,28–32]

Menstrual products and deodorants

There is insufficient evidence to make recommendations for or against the use of specific menstrual products, deodorants and antiperspirants.[33–35]

Psychosocial support measures

Indirect evidence indicates that psychological intervention is beneficial to people with different dermatoses, but specific studies are needed to confirm this in HS.[36]

Psychological intervention in the management of HS			
Strength		**Agreement**	
↔	May be considered	Strong consensus	34/34 (100%)

TOPICAL THERAPY – NONANTIBIOTICS

Resorcinol

Topical resorcinol 15% has been shown to be effective and well tolerated in reducing the size and number of non-fistulous HS lesions and decreasing pain and lesion duration.[37–40]

Mechanism

Resorcinol (m-dihydroxy benzene) is a phenolic compound with keratolytic, antipruritic and antiseptic activities. It is administered in an oil/water cream with emulsifying waxes; ingredients listed as cremor lanette, consisting of the following components: alcohol cetylicus et stearylicus emulsificans b (cetostearyl alcohol type b), acidum sorbicum (sorbates), cetiol V (decyloleat), sorbitolum liquidum cristallisabile (sorbitol) and aqua purificata (water). In Europe, it is not marketed in 15% concentration and has to be prepared as a compound.[39] The formulation package in aluminium tubes has shown the physicochemical and microbiological stability of resorcinol for 12 months at room temperature.[41]

Indication

Mild-to-moderate HS (according to the IHS4 classification) without draining tunnels/localized Hurley stage I and mild stage II. No formal studies or guidelines are available on the use of resorcinol in pregnancy.

Dosage and duration of treatment

Resorcinol 15% twice daily in a flare and once daily as a maintenance treatment for up to 16 weeks.

Response rate

In a single-centre cohort study of 32 patients, 68.8% reported a clinical response and 65.6% reported at least a 50% improvement compared with the DLQI baseline score.[39] A retrospective trial reported HiSCR response in 85.3% of patients treated with resorcinol versus 52% HiSCR responders with topical clindamycin.[42] Topical 15% resorcinol was also found to be associated with high patient treatment satisfaction in 92 patients with HS Hurley I and Hurley II, assessed by Treatment Satisfaction Questionnaire for Medication (TSQM).[40]

Treatment of mild-to-moderate HS (without tunnels) with resorcinol 15% peel			
Strength		**Agreement**	
↔	May be considered	Majority agreement	20/34 (59%)

Other therapies

In a case series, including 11 HS patients, azelaic acid was not effective in improving DLQI and NRS.[43]

TOPICAL ANTIBIOTICS

Clindamycin

Clindamycin is the only antibiotic that has been studied as a topical agent.[44,45]

Mechanism

Clindamycin binds to the 50S ribosomal subunit of bacteria, where it disrupts transpeptidation and subsequently protein synthesis in a similar manner to macrolides although not chemically related.

Indication

Mild-to-moderate HS (according to the IHS4 classification) without draining tunnels.

Dosage and duration of treatment

Clindamycin 1% gel/lotion/cream twice daily in a flare for up to 12 weeks. Treatment may be prolonged if clinically indicated.

Results

In a double-blinded randomized controlled trial of 27 Hurley stage I or mild stage II HS patients, topical clindamycin 0.1% exhibited a 4.5-fold stronger improvement than placebo ($p < 0.01$) on superficial lesions (folliculitis, papules and pustules). The effect on deep AN was very low if any.[44] In a double dummy controlled trial of 46 HS patients with Hurley stage I or II, no significant difference was found between topical clindamycin 1% and systemic tetracycline 2×500 mg/day over 3 months.[45]

Treatment of superficial HS lesions of mild-to-moderate HS (without draining tunnels) with clindamycin 1% gel/lotion/cream			
Strength		**Agreement**	
↔	May be considered	Majority agreement	20/34 (59%)

SYSTEMIC ANTIBIOTICS

Tetracyclines

The largest study on the efficacy of tetracyclines to date is a prospective, multicentre cohort study comparing oral tetracyclines with oral clindamycin and rifampicin.[46] Out of the included 283 patients, 103 received oral tetracyclines (tetracycline, $n = 42$; doxycycline, $n = 121$; minocycline, $n = 17$).

Mechanism

Tetracyclines bind to the 30S ribosomal subunit reversibly and prevent the binding of the amino acyl tRNA and thus translation.

Indication

Tetracyclines can be prescribed to mild-to-severe HS patients (according to the IHS4 classification).[46,47] They should not be administered to pregnant women or children younger than 9 years old due to risk of discoloration of permanent teeth.[48]

Dosage and duration of treatment

All tetracycline antibiotics are administered for a duration of 3 months.

Response rate

HiSCR achievement of tetracyclines ranges from 23.5% to 64.0% of patients.[46,47,49] A European cohort study has shown HiSCR achievement in 40.1% HS patients under tetracyclines.[46] Patient characteristics or disease severity were not associated with the attainment of HiSCR, the minimal clinically important differences for the DLQI and pain. A small study demonstrated that the efficacy of subantimicrobial,

modified-release doxycycline (40 mg/day) per os (p.o.) is similar to regular-release doxycycline (100 mg 2×/day) with, respectively, 64% and 60% of patients achieving HiSCR after 12 weeks of treatment.[49] Other tetracyclines, such as lymecycline (300 mg/day, $n = 45$), have been studied in smaller patients numbers and show similar efficacy compared with tetracycline or doxycycline.[47]

Tetracyclines as first choice HS treatment			
Strength		**Agreement**	
↑↑	Should be considered	Majority agreement	25/34 (74%)

Tetracycline antibiotics for a duration of maximum 3 months/course			
Strength		**Agreement**	
↑↑	Should be recommended	Consensus	30/34 (88%)

Interchangeable use of tetracyclines			
Strength		**Agreement**	
↑↑	Should be recommended	Majority agreement	25/34 (74%)

Clindamycin and rifampicin

Multiple studies have deemed combination treatment with clindamycin and rifampicin to be beneficial in HS.[50–52] However, the aforementioned prospective study by van Straalen et al.[46] demonstrated that clindamycin in combination with rifampicin shows similar efficacy as tetracyclines regardless of disease severity.

Mechanism

For clindamycin see chapter 'Topical antibiotics – Clindamycin'. Rifampicin inhibits DNA-dependent RNA polymerase activity in bacteria, by interacting with bacterial RNA polymerase. Moreover, it significantly inhibits IL-1β, IL-6, IL-8, IL-10 and TNF-α production in ex vivo HS lesional skin explants.[53] Rifampicin is a strong inducer of cytochrome P450 and may influence the metabolism and toxicity of other drugs metabolized by the same pathway, such as oral contraceptives. Combined treatment with rifampicin and clindamycin has been shown to significantly reduce the plasma concentration of clindamycin in patients with HS.[54] However, the clinical importance of this finding remains unknown.

Indication

Combination therapy with clindamycin and rifampicin p.o. may be considered for individual moderate-to-severe HS patients (according to the IHS4 classification).

Dosage and duration

In combination treatment, clindamycin and rifampicin are administered in a dosage of 2 × 300 mg/day p.o. each for the duration of 10–12 weeks.

Response rate

A European cohort study demonstrated a HiSCR achievement of 48.2% in 180 HS patients.[46] One study, including 60 patients, demonstrated no statistically significant difference in clinical response among patients treated with either clindamycin monotherapy ($n = 30$, HiSCR 56.5%) or combined treatment with clindamycin and rifampicin ($n = 30$, HiSCR 63.3%) after 8 weeks of treatment.[55]

The clindamycin and rifampicin combination in moderate-to-severe HS patients			
Strength		**Agreement**	
↑	Could be recommended	Consensus	27/34 (79%)

Clindamycin

Clindamycin monotherapy—p.o. or i.v.—may be considered instead of the combination of clindamycin and rifampicin.

Mechanism

See chapter 'Topical antibiotics – Clindamycin'.

Indication

Clindamycin p.o. monotherapy has been assessed in mild-to-severe HS patients and shows a significantly better response rate in mild-to-moderate patients (IHS4).[55,56] Clindamycin i.v. has been studied as a first choice treatment in therapy-naïve patients with moderate-to-severe HS.[9]

Dosage and duration of treatment

Clindamycin monotherapy has been assessed for the dosage of 2 × 300 mg/day p.o. for the duration of 12 weeks as well as 3 × 600 mg/day i.v. over 5 days.

Response rate

Reported HiSCR achievement to clindamycin p.o. monotherapy ranges from 56.5% to 61.8% in a single-centre prospective study with 30 patients and a retrospective study with

53 HS patients treated for 8 weeks.[55,56] In an observational retrospective study with 61 therapy-naïve patients, a 5-day loading dose of i.v. clindamycin (3 × 600 mg/day)—prior to 10–12 weeks of clindamycin–rifampicin combination treatment p.o.—resulted in a significant median 30% reduction of IHS4 and 47% of DLQI.[9]

Clindamycin p.o. as monotherapy			
Strength		**Agreement**	
↔	May be considered	Majority agreement	22/34 (65%)

Clindamycin i.v. as monotherapy (5 days) to quickly reduce inflammation			
Strength		**Agreement**	
↔	May be considered	Majority agreement	24/33 (73%)

Ertapenem

Mechanism

Ertapenem is a broad-spectrum i.v. β-lactam antibiotic belonging to a group of antibiotics known as carbapenems. It covers aerobic and anaerobic bacteria. Ertapenem is bactericidal as it binds to the penicillin-binding proteins that weaken or interfere with cell wall formation.

Indication

Ertapenem may be considered in severe HS patients (according to the IHS4 classification) and for down-staging prior to surgery.

Dosage and duration of treatment

One gram per day i.v. infusion as a 6-week course.

Response rate

Two retrospective studies involving a total of 66 patients have explored the use of ertapenem in the treatment of HS.[57,58] Ertapenem resulted in a significant reduction of the median Sartorius score from 49.5 (interquartile range [IQR] 28–62) to 19.0.[12–28,58] Altogether, 67% (29/43) and 26% (13/50) of Hurley stage I and II areas reached clinical remission in one study. Most patients received additional antibiotic as a consolidation treatment after ertapenem discontinuation. The other studies treatment duration varied from 8 to 128 days and ertapenem was administered in combination with concomitant medications.[57] The authors report a mean time relapse of 5.8 weeks (range, 1–22 weeks) after stopping ertapenem and without any consolidation or maintenance treatment. The majority of the patients (25/28, 89.3%) reported improvement of lesion drainage.

Ertapenem to reduce exuberant inflammation and drainage in severe HS			
Strength		**Agreement**	
↔	May be considered	Consensus	27/34 (79%)

Other antibiotics

A range of other systemic antibiotics have been suggested in case reports and in expert opinion, but none have been systematically evaluated even at the level of open prospective case series. The treatments mentioned below should currently be considered as experimental therapies.

Clindamycin and ofloxacin

The combination of clindamycin with ofloxacin has been retrospectively assessed among 65 patients with mild-to-moderate HS for a mean duration of 4.3 months (range, 1–20).[59] Four different dosages were used for clindamycin (600–1800 mg), and two different dosages for ofloxacin (200 or 400 mg) based on the patients' weight. Thirty-eight patients (58%) reported improvement of disease activity, with complete response for 22/65 (34%) and partial remission in 16/65 (25%). Clinical worsening was reported by seven (11%) patients and early cessation of treatment by 11 patients (17%). Twenty-eight per cent (18/65) of the patients reported side effects.

Rifampicin-moxifloxacin-metronidazole

Systemic treatment with a combination of rifampicin-moxifloxacin-metronidazole, either alone or preceded by systemic ceftriaxone in half of the patients, has been described as effective in an retrospective study of 28 patients with treatment-resistant moderate-to-severe disease.[60] Patients who showed response after 12 weeks of initial treatment were treated for an additional 12 weeks using a combination of moxifloxacin and rifampicin. The treatment led to complete response in 16/28 patients (57%). Main adverse effects were gastrointestinal symptoms and vulvovaginal candidiasis.

CONSIDERATION OF BACTERIAL RESISTANCE UNDER LONG-TERM ANTIBIOTIC TREATMENT

Long-term antibiotic treatment can lead to antibiotic resistance. This may pose a problem as international HS guidelines typically recommend antibiotic treatment for 10–12 weeks as first-line therapy in patients with mild-to-moderate disease severity and antibiotics are also intermittently used to control

flares.[1,2,7,61–67] Antibiotic treatment in HS is used with alleged anti-inflammatory properties,[50–52,68] but an antimicrobial effect cannot be ruled out, given the presence of a rich bacterial flora within lesions.[69–72] Whichever mechanism is related to efficacy, any antibiotic may induce resistance in patient's microbiome. World Health Organization Regional Office for Europe and the European Centre for Disease Prevention and Control consider the rising antimicrobial resistance (AMR) as a major public health concern.[73] Data on AMR in HS patients treated with antibiotic are scarce, and only a few evaluated AMR development after an antibiotic course in HS patients.[56,74]

In a cross-sectional analysis, Fischer et al. included 239 patients with bacterial data from HS lesions and concluded that antibiotic therapy for HS may induce AMR.[74] They found patients using topical clindamycin more likely to grow clindamycin-resistant *Staphylococcus (S.) aureus* in comparison with patients not using antibiotics (63% vs. 17%; $p=0.03$) and that ciprofloxacin induced ciprofloxacin and methicillin resistance in *S. aureus*, when compared with those who did not receive any antibiotic (100% vs. 10%; $p=0.045$). Trimethoprim/sulfamethoxazole-resistant *Proteus* species were also increased in patients using trimethoprim/sulfamethoxazole as compared with no antibiotic (88% vs. 0%; $p=0.001$). Surprisingly, no significant antimicrobial resistance was observed in patients treated with tetracyclines or oral clindamycin.[74] It has been suggested that adding a disinfectant may reduce the development of AMR.[75,76] Other studies examined the frequency of AMR in isolates from HS patients. The frequency range of AMR for different AB tested is broad (Table S1).[56,75,77–80] It is notorious that AMR differs between geographical regions due to different habits of antibiotic prescriptions and/or antibiotic restrictions.[73] General microbiological rules could be proposed to prevent or limit AMR. Taking into consideration HS severity, it is the prescribing physician's responsibility to measure benefits and risks of antibiotic treatment. In difficult cases, consultation of infectious diseases and/or microbiology experts is required.

Discontinuation of antibiotic treatment when it fails after several weeks			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	34/34 (100%)

Avoidance of low dosing regimen for induction treatment (high bacterial load at induction)			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	34/34 (100%)

Considering deleterious pharmacokinetic interaction (54,81)			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	34/34 (100%)

Adapted strategy to the bacterial load of lesions and disease severity (70)			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	34/34 (100%)

ANTI-INFLAMMATORY TREATMENT

Intralesional corticosteroids

Indication

Intralesional triamcinolone acetonide showed effectiveness in rapidly reducing inflammation associated with acute flares and in managing recalcitrant nodules and tunnels.[82]

Dosage and duration of treatment

Single triamcinolone acetonide 10–40 mg/mL injection in individual lesions was given either as monotherapy or in combination with systemic treatments.[83] Ultrasonography can be used to guide the injection of triamcinolone and to assess the response to treatment.[84] In case of no response, follow-up triamcinolone injections can be administered in periods ranging from 1 week and 3 months.[85]

Response rate

Effective clinical response, in terms of complete resolution of the lesions and significant improvement of erythema, suppuration or edema can be expected in 44–70% of the patients.[83] Significantly reduced patient-reported pain is usually observed within one day and the improvement in physician-assessed severity can be achieved within 7 days.[86]

Intralesional corticosteroids (in single lesions in mild-to-moderate HS)			
Strength		**Agreement**	
↔	May be considered	Majority agreement	16/32 (50%)

Systemic corticosteroids

Indication

High-dose systemic corticosteroids have been shown to be effective in treating acute flares but have been associated with exacerbations when tapering the dose.[87] Care should be taken during pregnancy due to the potential risk of neonatal adrenal suppression.[88]

Dosage and duration of treatment

Ten milligram per day prednisolone equivalent p.o. could be used as an adjunct treatment of refractory disease.[7] Short-term, higher dose prednisolone equivalent p.o. (0.5–0.7 mg/kg/day) may be effective in acute flares; the dose should be rapidly tapered.[82]

Response rate

Limited case reports and case series are available regarding the use of systemic corticosteroids in the treatment of HS. Eleven/13 patients with recalcitrant HS showed a clinical response to 10 mg/day prednisolone as an adjunct therapy, as evaluated by PGA at 2- to 4-week intervals.[89] In 16 patients with moderate-to-severe HS treated with prednisolone, at a median dose of 0.44 mg/kg/day for a median period of 30 days as an adjunct treatment for disease control or preoperative care, a HiSCR achievement of 70% and an IHS4 reduction in 40% of patients were reported.[90] In addition, a significant reduction in median pain NRS and DLQI was observed in 74% and 19% of patients, respectively. Three patients experienced a remarkable disease worsening after steroid cessation.

Dapsone

Mechanism

Dapsone (4,4′-diaminodiphenyl sulphone) is a sulphone drug with antibacterial and anti-inflammatory properties. Antibacterial activity is mediated through inhibition of dihydrofolic acid synthesis; the mechanism of anti-inflammatory activity is less well defined.

Indication

Patients with mild-to-moderate disease (according to the IHS4 classification). Therapy should be initiated where standard first or second-line agents fail. Dapsone is not teratogenic but should be avoided during breast feeding.

Dosage and duration of treatment

T–200 mg/day for a minimal duration of 3 months and a maximum reported range of 3–48 months.

Response rate

Current evidence for dapsone usage in HS is limited to case reports, case series and uncontrolled retrospective studies.[91]

Dapsone as a third-line treatment for mild to moderate HS			
Strength		**Agreement**	
↔	May be considered	Consensus	30/34 (88%)

Colchicine

Colchicine is a natural alkaloid extracted from plants of the lily family, including Colchicum autumnale.

Mechanism

Colchicine has both antimitotic and anti-inflammatory effects.

Dosage and duration of treatment

0.5–2.5 mg/day.[92]

Response rate

In an open prospective study with 20 patients, a combination of colchicine 0.5 mg/day and minocycline 100 mg/day led to improvement in every score after 3 months and the improvement persisted over time.[93] In a retrospective analysis of 44 patients divided into three groups (colchicine monotherapy 1 mg/day, colchicine and doxycycline 100 mg/day and colchicine and doxycycline 40 mg/day), colchicine was assessed effective both alone and in combination.[94]

Zinc gluconate

Mechanism

Zinc has antioxidant and immunomodulatory properties.[95]

Indication

Zinc may be considered as a second-line maintenance treatment in mild-to-moderate HS. Zinc supplementation can be administered in zinc deficient patients. A prospective case–control study showed significantly lower serum zinc levels in 122 HS patients with mild-to-moderate HS compared with 122 controls ($p < 0.001$).[96] Low zinc levels were also associated with more severe HS and lower DLQI.

Dosage and duration

90 mg/day zinc gluconate p.o. at initiation, may be lowered according to results and gastrointestinal tract side effects: long-term treatment.

Response rate

Several studies have shown that oral zinc gluconate may have a suppressive effect in HS lesions. In 22 patients with mild-to-moderate HS, eight complete remissions and 14 partial remissions were registered.[97] A combination of zinc gluconate 90 mg/day and topical triclosan 2% 2×/day was evaluated in a retrospective study in 66 patients with mild-to-moderate HS. After 3 months of treatment, a significant decrease in the median modified HS score and DLQI was observed ($p < 0.0001$ and $p = 0.0386$, respectively) with significant decrease in inflammatory nodules and flares, while tunnel count and visual analogue scale (VAS) did not change.[30] In a retrospective clinical study, 47 patients with mild-to-moderate HS were treated with 90 mg zinc gluconate and 30 mg of nicotinamide daily for 90 days. Significant reduction in the number and mean duration of acute flares, VAS, DLQI and IHS4 were observed at 12 and 14 weeks, compared with 45 patients in the control group without treatment ($p < 0.05$).[98] A combination of zinc gluconate (90 mg/day) and topical clindamycin did not show similar effectiveness in controlling HS flares like azithromycin and topical clindamycin in a prospective cohort study in eight female children with mild-to-moderate HS.[99]

Oral zinc gluconate as a second line treatment in patients with mild-to-moderate HS			
Strength		**Agreement**	
↔	May be considered	Majority agreement	19/32 (59%)

Ciclosporine

Mechanism

Ciclosporine is a calcineurin inhibitor with potent immunosuppressive activity. It specifically targets T lymphocytes, suppressing both the induction and proliferation of T-effector cells and inhibiting production of cytokines (TNF-α and IL-2).

Indication

Ciclosporine should be reserved to cases where failure of response to standard first-, second- and third-line therapies occurs.

Dosage and duration of treatment

Ciclosporine 2–6 mg/kg/day has been administered for variable duration (6 weeks–7 months).[100] There are limited data assessing appropriate dose or duration in HS treatment.

Response rate

An exploratory retrospective review of ciclosporine treatment in HS patients was performed at three centres between 2009 and 2012 with a 50% slight improvement in recalcitrant HS cases.[101]

Ciclosporine in the treatment of recalcitrant HS			
Strength		**Agreement**	
↔	May be considered	Majority agreement	17/34 (50%)

Immunoglobulin

Mechanism

γ-Globulin exhibits immune-modulatory actions.[102] Immunomodulation is primarily used to decrease inflammatory reactions by controlling various, mainly antibody-mediated, components of the immune mechanisms.

Indication

Chronic recalcitrant HS.

Dosage and duration of treatment

Human immunoglobulin administered at a dose of 12.38 mg/kg i.m. monthly for 1–15 months.

Response rate

In a monocentric, retrospective study with 63 HS patients, 37 (59%) showed overall improvement.[103] No improvement or worsening was seen in 3/63 (5%) patients (5%). A period without new lesions was achieved in 46/63 (73%) patients.

Intramuscular immunoglobulin as a third line treatment in patients with HS			
Strength		**Agreement**	
↓	Is not recommended	Majority agreement	23/32 (72%)

HORMONAL TREATMENT OF HS

There is an ongoing debate on the role of sex hormones in the pathogenesis of HS. Arguments in favour are that the first signs of the disease coincide with the start of the menstrual cycle and that many female patients experience perimenstrual flaring of the disease or during pregnancy.[104,105]

Hormonal antiandrogens

Limited clinical studies showed that antiandrogens, such as cyproterone acetate and oestrogens, improve HS, while progestogens induce or worsen a pre-existing HS due to their androgenic properties.[106–108]

Indication

Female patients with polycystic ovary syndrome (PCOS), menstrual abnormalities, signs of hyperandrogenism or upper normal or high serum levels of dehydroepiandrosterone, androstenedione and/or sexual hormone-binding protein.[109]

Response rate

The combined treatment with the antiandrogen, cyproterone acetate and ethinyl oestradiol on four women with long-standing HS controlled the disease successfully in all patients with 100 mg/day cyproterone acetate using the reversed sequential regimen, lowering the antiandrogen to 50 mg/day caused deterioration.[106] Further seven females receiving hormonal antiandrogens with 9-nortestosterone derivatives induced or exaggerated HS, whereas other contraceptives did not influence or improved HS at the same individuals.[107] A double-blind trial of two contraceptive pills, one containing 50 mg of cyproterone acetate and the other one norgestrel, showed no difference in the improvement observed in female patients with HS.[110]

Hormonal antiandrogens as an adjust treatment in female patients with HS and PCOS, menstrual abnormalities, signs of hyperandrogenism or upper normal or high androgen serum levels

Strength		Agreement	
↔	May be considered	Majority agreement	19/33 (58%)

Spironolactone

Spironolactone is a synthetic anti-mineralocorticoid with antiandrogen, gestagen, oestrogen and glucocorticoid effects.[111] It is more commonly known as a potassium-sparing diuretic compound.

Dosage and duration of treatment

100 mg/day (50–150 mg/day) spironolactone p.o. There is no standard dose for the treatment of HS. To limit side effects, a starting dose of 25 or 50 mg/day is subsequently increased after a few weeks. There is no enough evidence for recommendation in HS treatment.

Response rate

Responses to spironolactone are usually registered within 3 months.[111] A retrospective study of 67 women received 25–200 mg/day spironolactone (average dose 75 mg/day) followed for an average of 7 months exhibited improvement in pain, inflammatory lesion count and physician-assessed disease severity.

BIOLOGICS

Adalimumab

Mechanism

Adalimumab is a fully human monoclonal antibody corresponding to the human immunoglobulin IgG1. It binds with high affinity and specificity to soluble and membrane-bound TNF-α and blocks its biological activity.

Indication

Adalimumab is a European Medicines Agency (EMA)- and FDA-approved drug for the treatment of active moderate-to-severe HS indicated for patients >12 years with an inadequate response to conventional systemic HS therapy. Antibiotics may be continued during adalimumab treatment.

Dosage and duration of treatment

The approved dosage for HS is (a) for adults: adalimumab 160 mg on Day 1, 80 mg on Day 15 and from Day 29, 40 mg each week or 80 mg every 2 weeks. If adalimumab is discontinued, it can be reintroduced with 40 mg each week or 80 mg every 2 weeks. (b) For patients ≥12 years and ≥30 kg: 80 mg Day 1, followed by 40 mg every 2 weeks starting Day 8. If effect is not achieved, adalimumab can be administered at 40 mg each week or 80 mg every 2 weeks. Adalimumab is administered by subcutaneous (s.c.) injection. There is no dose adjustment for patients with obesity (>100 kg). In patients with less than 25% improvement in AN count after 12 weeks, treatment with adalimumab should be discontinued. For patients who do not achieve HiSCR, but achieve a 25%–50% improvement in AN count (partial response) after 12 weeks, continuation for 3 more months should be considered, since it has been shown that 73% of partial responders achieved HiSCR at Week 12.[112] Following discontinuation of treatment, recurrence can occur after a median of 11–12 weeks.[10]

Response rate

In a three arm RCT with 154 patients consisting of a double-blind phase and an open-label phase, patients were assigned to adalimumab 40 mg every week (after 160 mg at Week 0 and 80 mg at Week 2), 40 mg every other week (after 80 mg at Week 0) or placebo. At Week 16, the proportion of patients achieving a HS-PGA score of clear, minimal or mild, with at least a 2-grade improvement relative to baseline, was 17.6%, 9.6% and 3.9% for every week, every other week and placebo, respectively (every week group vs. placebo, $p = 0.025$).[113] Significant improvements were also seen in secondary outcomes, including VAS pain and DLQI for the every week group. A decrease in response was registered after the switch from every week to every other week in the open-label period. The two phase 3, double-blinded RCT PIONEER-I and II and their open-label extension (OLE) trial with 633 patients assigned in a 1:1 ratio to 40 mg adalimumab weekly or matching placebo for 12 weeks in the first period and reassignment to adalimumab at a weekly or every-other-week dose or to placebo for 24 weeks revealed a HiSCR achievement of 41.8% versus 26.0% in PIONEER-I ($p = 0.003$) and 58.9% vs. 27.6% in PIONEER-II ($p < 0.001$; patients also received systemic antibiotics in both study arms). Patients receiving adalimumab had significantly greater improvement than the placebo groups in rank-ordered secondary outcomes (lesions, pain and the modified Sartorius score for disease severity) at Week 12 in PIONEER-II only. In a study of 2 years, continuous treatment maintained a level of consistent effectiveness in responders with an acceptable safety profile.[112] In the PIONEER-I dataset, 65/144 (45%) of patients treated with adalimumab versus 41/145 (28%) with placebo ($p = 0.003$) and in the PIONEER-II dataset, 91/149 (61%) of patients treated with adalimumab versus 43/140 (30%) with placebo achieved IHS4-55.[21]

Adalimumab as a first line treatment for patients (>12 years) with moderate-to-severe HS and an inadequate response to conventional systemic HS therapy			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	34/34 (100%)

Adalimumab for pediatric patients (>12 years) with moderate-to-severe HS and an inadequate response to conventional systemic HS therapy			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	34/34 (100%)

Adalimumab biosimilars

In recent years, the use of approved adalimumab biosimilars as alternative to the originator for the treatment of moderate-to-severe HS has increased.[114] Due to their pharmaco-economic effects, the breakthrough of biosimilar drugs has made the overall use of adalimumab more accessible. The switch from the adalimumab originator to biosimilars, taking medical aspects into account, has now been sufficiently analysed.[115–118] In well-controlled patients, the switch from the adalimumab originator to a biosimilar might create problems with respect to effectiveness and compliance. Therefore, the therapy change in patients in remission with a maintenance therapy is viewed critically. A careful integration of pharmaco-economic measures with a thorough assessment of the risk–benefit ratio of a non-medical switch from originators to biosimilars is still indispensable to offer the best therapeutic option to every HS patient.

Intra-class switching to other anti-TNF agents in secondary non-responders			
Strength		**Agreement**	
↔	May be considered	Strong consensus	29/29 (100%)

Infliximab

Mechanism

Infliximab is a chimeric (mouse/human) monoclonal antibody. It binds specifically to both soluble and transmembrane, receptor-bound TNF-α. Soluble TNF-α is ligated and its proinflammatory activity is neutralized. Infliximab has a serum half-life of about 8 to 9.5 days. The elimination period is up to 6 months. Infliximab is not approved for the treatment of HS by the EMA or the FDA.

Indication

Moderate-to-severe HS (according to the IHS4 classification). Infliximab is not approved for the treatment of HS by the EMA or the FDA.

Dosage and duration of treatment

Infliximab 5 mg/kg i.v. at Weeks 0, 2 and 6, and subsequently every 8 weeks.

Response rate

In a double-blinded RCT with 38 HS patients, 20 patients received infliximab (5 mg/kg at Weeks 0, 2 and 6, and subsequently every 8 weeks) or placebo over 52 weeks. After 8 weeks, the double-blind phase was followed by an open-label phase. Patients taking placebo given the opportunity to cross-over. More patients in the infliximab group showed a ≥50% decrease from baseline in HS severity score (a non-validated composite scoring system), when compared to placebo at Week 8, although this difference in improvement was not significant (27% vs. 5%, $p = 0.092$).

However, infliximab was significantly more effective on PGA, VAS, DLQI and in producing 25%–50% improvement on HS severity score. Also, a significant reduction in inflammatory markers was observed at Week 8.[119] Infliximab monotherapy was well tolerated and a greater number of adverse events occurred in the placebo group. Long-term use evidence (1 year) is only based on a single-centre case series of eight patients with moderate-to-severe HS.[120] Infliximab resulted in significant reduction of the number of involved sites ($p < 0.001$) and flares ($p < 0.05$).

Infliximab as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory

Strength		Agreement	
↑	Could be recommended	Majority agreement	17/34 (50%)* *Chairman's vote

Etanercept

Mechanism

Etanercept is a fusion recombinant protein, which fuses the TNF receptor and inhibits TNF-α binding.

Indication

Moderate-to-severe HS (accordin.

Dosage and duration of treatment

Etanercept 50 mg 2×/week s.c.

Response rate

In a prospective, double-blind, cross-over RCT of 20 HS patients treated with etanercept (50 mg 2×/week s.c.) for 12 weeks, no difference compared with placebo could be detected.[121]

Etanercept in the treatment of moderate-to-severe HS as a second line biologic treatment if the result of first-line biologic treatment is unsatisfactory

Strength		Agreement	
↓	Is not recommended	Consensus	28/34 (82%)

Certolizumab pegol

Mechanism

Certolizumab pegol is a recombinant, humanized monoclonal antibody against TNF-α.

Indication

Active moderate-to-severe HS.

Dosage and duration of treatment

Certolizumab pegol 400 mg s.c. every 2 weeks.

Response rate

In a retrospective series of 11 patients unresponsive to adalimumab, certolizumab pegol led to the achievement of the HiSCR in 54.5% of participants at Week 12; however, the level of evidence is low.[122]

Certolizumab pegol in the treatment of moderate-to-severe HS as a second line biologic treatment if the result of first-line biologic treatment is unsatisfactory

Strength		Agreement	
↓	Is not recommended	Strong consensus	28/29 (97%)

Secukinumab

Several studies have demonstrated increased levels of Th17 cells and overexpression of IL-17 in HS, providing a rationale for IL-17 inhibition as a therapeutic strategy.[123–126]

Mechanism

Secukinumab is a human monoclonal antibody against IL-17A.

Indication

Secukinumab is a medicinal product approved by the EMA and the FDA for the treatment of adult patients with moderate-to-severe active HS with inadequate response to conventional systemic HS therapy.[11]

Dosage and duration

The approved dosage for HS is 300 mg with initial doses in the Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance doses. Based on the clinical response, the maintenance dose may be increased to 300 mg every 2 weeks. Secukinumab is administered as a s.c. injection.

Response rate

Secukinumab was evaluated in two phase 3 RCT for the treatment of 1084 patients with moderate-to-severe HS (SUNSHINE

and SUNRISE). The primary endpoint of both trials was HiSCR at 12 weeks. In the SUNSHINE study, 82/181 (45.0%) of patients treated with secukinumab 300 mg every 2 weeks s.c. achieved HiSCR compared with 61/180 (33.7%) of placebo patients ($p=0.0070$).[11] In the SUNRISE study, 76/180 (42.3%) of patients treated with secukinumab 300 mg every 2 weeks s.c. achieved HiSCR compared with 57/183 (31.2%) of placebo patients at Week 12 ($p=0.015$). Patient responses were sustained up to the end of the trials at Week 52. In the SUNSHINE study, secukinumab at a dose of 300 mg every 4 weeks s.c. did not meet the primary endpoint (HiSCR at 12 weeks) compared with placebo, but the primary endpoint was met in the SUNRISE study where 46.1% achieved HiSCR compared with 31.2% of placebo patients ($p=0.0022$).[11] In a post hoc analysis of the same studies, secukinumab was more effective than placebo regardless of prior biologic exposure after evaluation by both HiSCR and IHS4-55.[127] [Correction added on 21 Janaury 2025, after first online publication: "SUNRINE" and "SUNSHIINE" have been revised to "SUNRISE" and "SUNSHINE".]

Secukinumab as a first line biologic treatment in patients with moderate-to-severe HS and an inadequate response to conventional systemic HS therapy			
Strength		**Agreement**	
↑↑	Should be recommended	Consensus	32/35 (91%)

Bimekizumab

Mechanism

Bimekizumab is a humanized monoclonal IgG antibody of full length selectively inhibiting both IL-17 and IL-17F. The inhibition of both cytokines might produce an additional effectiveness in HS.[128]

Indication

Bimekizumab is a medicinal product approved by the EMA for the treatment of adult patients with moderate-to-severe active HS with inadequate response to conventional systemic HS therapy.[12]

Dosage and duration of treatment

The approved dose is 320 mg s.c. every 2 weeks for 16 weeks and then every 4 weeks after. Bimekizumab is administered as a s.c. injection.

Response rate

Bimekizumab was evaluated in a phase 2 proof-of-concept RCT. At Week 12, in 46 patients, bimekizumab at a dose of 320 mg s.c. every 2 weeks, 57.3% achieved HiSCR compared with 26.1% of placebo patients. Improvement in the IHS4 was seen at Week 12 with bimekizumab (40.0 → 16.0) compared with placebo (50.0 → 40.2).[128] Bimekizumab was further assessed in two identically designed phase 3 RCTs for the treatment of 1014 patients with moderate-to-severe HS (BE HEARD I and II). Patients aged ≥18 years with moderate-to-severe HS were randomly stratified by worst Hurley stage and systemic antibiotic use at baseline to receive bimekizumab 320 mg every 2 or 4 weeks to Week 16, then bimekizumab 320 mg every 4 weeks to Week 48; or placebo to Week 16, then bimekizumab 320 mg every 2 weeks. A higher HiSCR achievement rate was observed with bimekizumab every 2 weeks versus placebo in both trials: 138/289 (48%) patients under bimekizumab versus 21/72 (29%) under placebo in BE HEARD I ($p=0.0060$) and 151/291 (52%) patients under bimekizumab versus 24/74 (32%) under placebo in BE HEARD II ($p=0.0032$). In BE HEARD II, HiSCR was also achieved in the group who received bimekizumab every 4 weeks (54%) versus (32%) under placebo ($p=0.0038$). Responses were maintained or increased to Week 48.

Bimekizumab as a first line biologic treatment in patients with moderate-to-severe HS and an inadequate response to conventional systemic HS therapy			
Strength		**Agreement**	
↑↑	Should be recommended	Consensus	32/35 (91%)

Brodalumab

Mechanism

Brodalumab is a human, monoclonal antibody against the IL-17 receptor.

Indication

Moderate-to-severe HS (according to the IHS4 classification). Brodalumab is not approved for the treatment of HS by the EMA or the FDA.

Dosage and duration of treatment

Brodalumab 210 mg s.c. every 2 weeks.

Response rate

In participants of two open labelled studies with draining tunnels, administration every 2 weeks resulted in rapid reduction in acute symptoms with slow recurrence of tunnel drainage and pain.[129,130]

Brodalumab as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↔	May be considered	Consensus	32/34 (94%)

Anakinra

IL-1 is a proinflammatory cytokine that has been shown to be highly upregulated in lesional HS skin, probably as a result of activation of the inflammasome, making it a target for treatment in HS.[131]

Mechanism

Anakinra is a recombinant IL-1 receptor antagonist. It blocks the biological activity of naturally occurring IL-1 by competitively blocking the binding of both IL-1α and IL-1β to the IL-1 type 1 receptor.

Indication

Moderate-to-severe HS (according to the IHS4 classification). Anakinra is not approved for the treatment of HS by the EMA or the FDA.

Dosage and duration of treatment

100 mg/day s.c.

Response rate

In a randomized placebo-controlled trial of 12 weeks treatment and 12 weeks of follow-up, 10 HS patients received anakinra 100 mg/day s.c. and 10 patients placebo.[132] HiSCR was achieved in 6/9 patients (67%) in the anakinra group versus 3/10 patients (30%) in the placebo group ($p = 0.04$). In addition, the treatment group showed a significantly longer time to the first new relapse after treatment ($p = 0.01$).

Anakinra as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↔	May be considered	Majority agreement	20/34 (59%)

Bermekimab

Mechanism

Bermekimab is a human monoclonal antibody that neutralizes IL-1α by binding this cytokine with high affinity, thereby neutralizing IL-1α activity.

Indication

Active moderate-to-severe HS.

Dosage and duration of treatment

Bermekimab 7.5 mg/kg i.v. every 2 weeks/400 mg s.c. weekly.

Response rate

Two open-label studies used bermekimab for treatment of moderate-to-severe HS. In a phase 2 double-blind RCT with 20 patients with refractory HS or ineligible for adalimumab, bermekimab was administered i.v. every 2 weeks at a dose of 7.5 mg/kg. 6/10 (60%) patients treated with bermekimab and 1/10 (10%) patients receiving placebo achieved HiSCR ($p = 0.035$).[133] In a phase 2 open-label study with 24 patients who failed anti-TNF-α treatment and 18 treatment naïve patients, 63% and 61% under bermekimab achieved HiSCR.[134] However, a subsequent phase 2 RCT, including 144 patients, was prematurely stopped after interim analysis because futility criteria were met.[135]

Ustekinumab

Mechanism

Ustekinumab is a recombinant, fully human IgG1 antibody. It binds with high specificity and affinity to the common p40 subunit of the cytokines IL-12 and IL-23.

Bermekimab as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↓	Is not recommended	Majority agreement	23/34 (68%)

Indication

Moderate-to-severe HS (according to the IHS4 classification). Ustekinumab is not approved for the treatment of HS by the EMA or the FDA.

Dose and duration of treatment

Ustekinumab 45 mg/week s.c. (in patients with a body weight >100 kg, 90 mg/week s.c.) at Weeks 0, 4, 16 and 28.

Response rate

In an open-label study, 12 HS patients were treated with 45 or 90 mg ustekinumab s.c. at Weeks 0, 4, 16 and 28 and presented a 82% moderate-to-marked improvement of the modified

Sartorius score and 47% HiSCR achievement at Week 40.[136] In a case series of 10 patients, a PGA improvement was observed in 7/10 (70%) patients and an improvement in the NRS pain 8/10 (80%).[137] A 50% HiSCR has been documented across several studies on moderate-to-severe, mostly adalimumab-resistant HS patients.[136,138,139] A retrospective series of 10 patients, of whom 8 had previously failed adalimumab, revealed a 90% HiSCR50 at a mean response time of 4.7 months,[140] possibly indicating that a more prolonged time may be needed to observe ustekinumab full effect. In a systematic review, clinical improvement in disease severity was reported in 34/75 (76%) patients and symptomatic improvement in 38/45 (84%).[137]

Ustekinumab as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↔	May be considered	Majority agreement	20/32 (63%)

Guselkumab

Mechanism

Guselkumab, a monoclonal antibody that binds to the p19 subunit of IL-23.

Indication

Active moderate-to-severe HS.

Dosage and duration of treatment

Guselkumab 200 mg s.c. or 1200 mg i.v. every 4 weeks.

Response rate

In a phase 2, multicentre, double-blind, proof-of-concept RCT 181 HS patients with moderate-to-severe HS for ≥1 year were randomized to guselkumab 200 mg s.c. every 4 weeks through Week 36, guselkumab 1200 mg i.v. every 4 weeks for 12 weeks and then switched to s.c. guselkumab or placebo.[141] Guselkumab s.c., i.v. and placebo achieved a HiSCR in 50.8%, 45.0% and 38.7% of the patients at Week 16, respectively, and no clear differences were recorded at Week 40. In a retrospective series, guselkumab 100–200 mg every 6–8 weeks led to the achievement of the HiSCR in 63.6% of 11 bio-experienced patients with a mean drug survival of more than 2 years.[142]

Guselkumab as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↓	Is not recommended	Majority agreement	16/32 (50%)

Risankizumab

Mechanism

Risankizumab is a humanized monoclonal antibody that targets IL-23A.

Indication

Active moderate-to-severe HS.

Dosage and duration of treatment

Risankizumab 150 mg at Week 0, 4 and every 12 weeks.

Response rate

Risankizumab was reported in several case reports to be effective in patients failing to respond to other biologics, including adalimumab and secukinumab.[143] However, a phase 2 RCT did not appear to be an efficacious treatment for moderate-to-severe HS.[144]

Risankizumab as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↓	Is not recommended	Strong consensus	29/29 (100%)

Spesolimab

Mechanism

Spesolimab is an anti-IL-36 receptor monoclonal antibody that selectively inhibits IL-36 signalling.

Indication

Moderate-to-severe HS (according tio the IHS4 classification) with draining tunnels. Results of phase III studies are awaited. Spesolimab is not approved for the treatment of HS by the EMA or the FDA.

Dosage and duration of treatment

A double-blind RCT proof-of-clinical-concept study was conducted with 52 moderate-to-severe HS patients randomized (2:1) to receive a loading dose of 3600 mg spesolimab i.v. (1200 mg at Weeks 0, 1 and 2) or matching placebo, followed by maintenance with either 1200 mg s.c. every 2 weeks from Weeks 4 to 10 or matching placebo.[145]

Response rate

At Week 12, no difference in total inflammatory AN count between spesolimab and placebo was detected. However, there was greater numerical improvement in the spesolimab arm, as measured by IHS4 (13.9, 95% CI −25.6 to −2.3), percentage change from baseline in draining tunnel count (−96.6%, 95% CI −154.5 to −38.8) and the proportion of patients achieving a draining tunnel count of 0 (18.3%, 95% CI −7.9 to 37.5).

Spesolimab as a second line biologic treatment in patients with moderate-to-severe HS with draining tunnels if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↔	May be considered	Majority agreement	22/35 (63%)

Povorcitinib

Mechanism

Povorcitinib is an oral, selective Janus kinase (JAK)1 inhibitor with approximately 52-fold greater selectivity for JAK1 versus JAK2.[146] It was shown to regulate genes and impacted JAK/STAT signalling transcripts downstream of TNF-α signalling or those regulated by tumour growth factor (TGF)-β.[147]

Indication

Moderate-to-severe HS (according to the IHS4 classification). Results of phase III studies are awaited. Povorcitinib is not approved for the treatment of HS by the EMA or the FDA.

Dosage and duration of treatment

Two phase 2 dose-escalation RCTs were conducted in 35 and 209 moderate-to-severe HS patients randomized to povorcitinib 15–180 mg/day or placebo for 8–12 weeks with a 30-day safety follow-up period at the end of treatment.[146,148]

Response rate

Seventeen (65%) patients receiving povorcitinib versus four (57%) patients receiving placebo achieved HiSCR at Week 8 in the first study.[146] The IHS4 mean changes from baseline at Week 8 were −9.4, −21.4 and − 16.1 for patients treated with 60, 120 and 180 mg povorcitinib versus −10.7 for the placebo group. In the second study, povorcitinib significantly reduced AN count from baseline at Week 12 (mean change: 15 mg, −5.2 $p = 0.0277$; 45 mg, −6.9, $p = 0.0006$; 75 mg, −6.3 $p = 0.0021$) versus placebo (−2.5). More povorcitinib-treated patients achieved HiSCR at Week 16 (15 mg, 48.1%, $p = 0.0445$; 45 mg, 44.2%, $p = 0.0998$; 75 mg, 45.3%, $p = 0.0829$) versus placebo (28.8%).[148] A total of 60.0% and 65.4% of povorcitinib- and placebo-treated patients had adverse events.

Povorcitinib as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↔	May be considered	Consensus	31/34 (91%)

Upadacitinib

Mechanism

Upadacitinib is an oral selective JAK1 inhibitor with high selectivity for JAK1 and its signal transduction molecules.

Indication

Moderate-to-severe HS (according to the IHS4 classification). No phase II or III studies have been published. Upadacitinib is not approved for the treatment of HS by the EMA or the FDA.

Dosage and duration of treatment

Upadacitinib 15 mg/day up to Week 4. If the clinical response is not sufficient after 4 weeks, treatment doses might be increased to 30 mg/day.[149]

Response rate

In a retrospective cohort study of 20 patients with moderate-to-severe HS treated with upadacitinib monotherapy, 15 patients (75%) achieved HiSCR at Week 4, growing up to 100% at Week 12 with the results being maintained up to Week 24.[149] HiSCR75 was achieved in six patients (30%) at Week 4 and 19 patients (95%) at Week 12; this result was maintained up to Week 24. HiSCR90 was achieved in four patients (20%) at Week 4 and increased to six patients (30%) at Week 12; these results were maintained to Week 24.

Upadacitinib as a second line biologic treatment in patients with moderate-to-severe HS if the result of first-line biologic treatment is unsatisfactory			
Strength		**Agreement**	
↔	May be considered	Majority agreement	22/35 (63%)

ELIGIBILITY FOR BIOLOGICS AND ADVANCED MOLECULES

Treatment of HS includes the use of biologic and small molecule drugs for patients with moderate and severe forms of disease. Identifying patients who are candidates for this type of treatments is important to avoid delays in treatment or under treatment that could lead to disease progression or reduced effectiveness.[150,151] The prescription of biologic drugs or advanced therapies/small molecules should always be carried out in accordance with the indications in the drug label and the therapeutic algorithm described in this guide, if in any case these conflict with the following eligibility criteria, the information in the drug label will prevail.

The presence of one or more of the following criteria may be used to identify patients who are candidates for treatment with biologics and advanced molecules (Table 2).[4,6,113,151–155] These criteria should serve as a generic guideline; each case should be analysed individually to choose the most beneficial treatment modality for the patient according to his or her clinical characteristics and personal preferences.

RETINOIDS

Isotretinoin

Mechanism

The main activity of isotretinoin in HS might be the prevention of an affected pilosebaceous unit from being occluded by ductal hyper-cornification. In addition, isotretinoin has been shown to have anti-inflammatory properties.[156] It might directly modify monocyte chemotaxis and exert secondary effects with regard to anti-keratinizing action and avoidance of hair follicle rupture. Reduction in sebaceous gland size and inhibition of sebaceous gland activity (responsible for the rapid clinical improvement observed in acne vulgaris) seem not to be of relevance in the treatment of HS as an absence or reduced volume of the sebaceous glands are observed in HS.[157]

TABLE 2 Eligibility criteria for biologics and advanced molecules.

Criteria	Value	References
Moderate-to-severe objective disease severity	IHS4 ≥4 or HS-PGA ≥3 (moderate) or Refined Hurley: IC, IIB, IIC, III or Increase in Hurley stage	[4,6,113,151]
Significant impairment of quality of life	DLQI >10 or HS-QoL >20	[152,153]
Clinical signs of unstable/progressive disease	Several outbreaks per year or Rapidly progressive disease or Extensive disease	[154]
Special clinical scenarios	Special locations: genital area, face, scalp, neck or Signs of local complications: lymphedema	[155]

Indication

Its usage in HS is often disappointing and the reported data are inconsistent.[158]

Dosage and duration of treatment

0.5–1.2 mg/kg/day administered within the period of 4–12 months.[158–164]

Response rate

Overall 112/174 (64.4%) non-responders were reported.[158–164] The presence of acne vulgaris or a history of previous acne had no impact on outcome.[158] The observed moderate-to-significant response among the rest of the patients was mainly restricted to these with mild HS. Moreover, approximately 13% of responders relapsed within a couple of months after cessation of the treatment. Poor response rate and loss of treatment motivation led to 20/68 (29.4%) drop-outs.[160] In a retrospective study with 102 patients, the overall drug survival of isotretinoin ($n = 66$) at 12 and 24 months was 44.2% and 15.5%, respectively.[165] Termination of treatment was mostly due to ineffectiveness (26%). Of the 39 and 25 patients of two further retrospective studies, 14 (35.9%) and 9 (36%) patients reported a beneficial response to isotretinoin.[166,167] In a current study with 82 HS patients, 10 (12.2%) reported that their acne was aggravated while taking isotretinoin, while 72 (87.8%) that their acne severity did not change.[168] Among the 10 HS patients whose acne worsened with isotretinoin, eight (80%) exhibited a conglobate phenotype. In addition to the conglobate acne phenotype, body mass index (BMI) >25 kg/m^2 increased the risk of worsening therapeutic outcome in the multivariate analysis.

Isotretinoin as a third line treatment in patients with mild-to-moderate HS			
Strength		**Agreement**	
↓	Is not recommended	Majority agreement	17/32 (53%)

Acitretin

Mechanism

Acitretin is a metabolite of etretinate and has replaced it in the treatment of various skin disorders since it is equally effective and has a much shorter elimination half-life. Acitretin reduces the keratinocyte rate of proliferation and dermal and epidermal inflammation by inhibiting polymorphonuclear cell chemotaxis and release of proinflammatory mediators.[169]

Indication

Acitretin might be used in early HS stages and in the presence of prominent hyperkeratotic follicular lesions.[170,171]

Dosage and duration of treatment

Acitretin 0.25–0.50 mg/kg/day for 3–12 months.

Response rate

In three studies with 28 patients on acitretin therapy, significant improvement was assessed in 17 (60.7%) patients.[170–172] Improvement on patients' quality of life detected by DLQI and hidradenitis suppurativa severity index (HSSI) was also observed after 6 months of treatment.[171] In a retrospective study with 102 patients, the overall drug survival of acitretin ($n = 36$) was 42.0% at 12 months and 37.4% at 24 months and was predominantly determined by ineffectiveness (28%).[165] Interestingly, the folliculitis phenotype was associated with prolonged drug survival time for acitretin treatment relative to the regular phenotype. In another retrospective cohort study with 62 patients with moderate-to-severe HS, a significant decrease in the IHS4 was found over time. Higher basal IHS4, family history of HS, follicular phenotype and history of follicular plugging conditions were potential predictors of response.[173]

Acitretin as a third line treatment in patients with moderate-to-severe HS and in certain hyperkeratotic conditions (scarring folliculitis)

Strength		Agreement	
↔	May be considered	Majority agreement	19/32 (59%)

ANALGESICS

Pain is the main symptom in HS disease and relief of this pain should be the primary objective of all treatments, as well as clinical improvement of lesions. No randomized controlled trials with analgesics for HS have been published. More than only a symptomatic therapy purely against pain, an efficient treatment targeted against HS disease itself should be preferred, since it seems more efficacious in the long and short term on the pain component. However, before these treatments can completely remove pain in HS patients, symptomatic analgesia might be useful.

Acetaminophen (paracetamol)

Indication

This molecule should always be tried in the first place for pain relief, due to its good tolerance profile and low number of contraindications. However, it may be insufficient for relieving the important pain encountered by severe HS patients, justifying combinations of acetaminophen with codeine and/or caffeine to increase efficacy.

Dosage and duration of treatment

Acetaminophen (paracetamol) 3 g/day p.o. in 3–6 intakes.

Acetaminophen (paracetamol) for the relief of pain in patients with HS

Strength		Agreement	
↑	Could be recommended	Majority agreement	16/32 (50%)* *Chairman's vote

Non-steroidal anti-inflammatory drugs (NSAID)

Indication

There is no proof of the efficacy of NSAID in HS. However, these molecules are regularly used by HS patients.

Response rate

The absence of evidence for their efficacy, the presence of numerous bacteria within HS lesions[71,174] and the cardiovascular and infectious risks of these medications indicate an individual, restrictive use of these analgesics for HS pain.

Non-steroidal anti-inflammatory drugs for the treatment of HS pain

Strength		Agreement	
↔	May be considered	Majority agreement	20/32 (63%)

Selective serotonin reuptake inhibitors (SSRI/antidepressants)

Indication

Duloxetine is an SSRI/selective serotonin noradrenalin reuptake inhibitor (SSNRI) that is used to treat major depressive disorders, general anxiety disorders, painful peripheral neuropathy, fibromyalgia, chronic musculoskeletal pain and chronic lower back pain.[175]

Venlafaxine has not been studied for HS pain.[176]

Dosage and duration of treatment

Duloxetine: 60 mg/day. *Venlafaxine*: 75 mg/day (maximum 375 mg/day); possibility to dose increase, taking into account safety profile and tolerability.

Response rate

The positive effect on both pain and depression might be beneficial for HS patients who are more likely to be depressed than case–control patients. The result of treatment has to be assessed after 2 months of treatment.

SSRI/antidepressants for the relief of pain in patients with HS			
Strength		**Agreement**	
↓	Is not recommended	Consensus	29/34 (85%)

Pregabalin/gabapentin

Mechanism

Gabapentin and pregabalin bind to the α2δ subunit of the voltage-dependent calcium channel in the central nervous system and affect γ-aminobutyric acid (GABA) levels. They decrease the release of neurotransmitters, including glutamate, noradrenaline, substance P and calcitonin gene-related peptide.

Indication

Gabapentin and pregabalin are used to relieve neuropathic pain.[177,178] They change neural thresholds, thereby decreasing pain.

Dosage and duration of treatment

The gabapentin starting dose is 2 × 50 mg/day (300 mg/day on Day 1, 600 mg/day on Day 2, 900 mg/day on Day 3, divided into three doses). Additional titration to 1800 mg/day is advisable for greater efficacy. Doses up to 3600 mg/day can be required in some obese patients. Pregabalin starting dose in HS patients is 50 to 2 × 50 mg/day, to increase gradually to 2 × 100 mg/day. The effective dose should be individualized.

Response rate

Long-term trials have shown continued effectiveness without development of tolerance. Pregabalin produces less severe cognitive and psychomotor impairment and has also a low potential for abuse and dependence and may be preferred over the opiates.

Pregabalin/gabapentin for the relief of pain in patients with HS			
Strength		**Agreement**	
↔	May be considered	Majority agreement	20/34 (59%)

Opiates

Indication

No clinical evidence exists for the use of opioids in the amelioration of pain in HS. Their use should be restricted and limited to cases where all other painkillers have failed. Codeine should be the first treatment option for this drug class if required. Hydrocodone may also be an option.

Use of opiates for the relief of pain in patients with HS			
Strength		**Agreement**	
↓	Is not recommended	Majority agreement	19/34 (56%)

Topical analgesics

Diclofenac

Dosage and duration of treatment

The topical preparations are diclofenac sodium 1.5% topical solution, diclofenac sodium 1% gel and a diclofenac hydroxyethylpyrrolidine 1.3% patch. Gentle rubbing in diclofenac 1% gel for 45 sec seems to increase its penetration into the epidermis. Duration should be 1–2 weeks.

Xylocaine

Indication

Temporary relief of pain and itching. Liposomal or micronized versions of xylocaine seem to maximize cutaneous effects and minimize systemic effects.

Dosage and duration of treatment

Topical xylocaine 1 or 2×/day is a mainstay of short-term (1–2 h) topical pain treatment.[179]

Capsaicin

Mechanism

Capsaicin selectively binds to the vanilloid receptor 1 primarily expressed on C-nerve fibres that release substance P.[180]

Dosage and duration of treatment

Maximum 3 to 4×/day at the affected area.

Application of topical analgesics for the relief of pain in patients with HS			
Strength		**Agreement**	
↓	Is not recommended	Majority agreement	24/34 (71%)

Given the lack of RCT for HS pain management and the disappearance of pain with HS efficient treatments an early management of HS and a cautious and limited use of all analgesics weighing their benefits and risks			
Strength		**Agreement**	
↑↑	Should be recommended	Consensus	29/34 (85%)

EXPERIMENTAL THERAPIES

Photodynamic therapy (PDT)

Mechanism

The mechanism of action of PDT for HS remains largely unknown. Indeed, PDT has (i) a direct cytotoxic effect on cells, (ii) antimicrobial effects and (iii) a role in the expression of anti-inflammatory cytokines.[181,182]

Response rate

PDT has been used to treat HS with conflicting results.

Blue light PDT

Three studies evaluated the use of blue light PDT with 20% 5-aminolevulinic acid (ALA) in 18 patients after an incubation period ranging from 15 min to 1.5 h.[183–185] Complete response was assessed in three (16.7%) patients.[185]

Red light PDT

Five studies with 21 patients have evaluated the use of red light PDT applying 5% to 20% ALA. Six (28.6%) patients experienced a moderate improvement with some of them relapsing after treatment discontinuation.[186–190] In a study using methylene blue in nanosomes and intense pulsed light with 630 nm filter as a light source, promising results were shown in 11 patients.[191] Another study with six patients used methyl aminolevulinate and red light as light source with an incubation period ranging from 3 to 4 h leading to marked or moderate response in five out of six patients.[192]

Intralesional PDT (iPDT)

The use of PDT with a 630 nm intralesional diode and 1%–5% ALA was evaluated in four studies (three retrospective, one open prospective) with 110 patients.[190–193] In 53/68 (83.8%), moderate to complete remission was achieved. In 42 patients, a high percentage of lesion resolution or improvement was observed.[193] Two further studies used intralesional methylene blue 1% solution as photosensitizer, injected into HS lesions with ultrasonography guidance in 48 patients and illuminated with a 635 nm red light-emitting diode lamp after an incubation period of 15 min.[194,195] In the first study, 5/7 patients (71%) improved and maintained HS remission of HS in the treated area.[194] In the second study, a reduction of ≥75% in the maximum lesion diameter was reported in 24/41 (58.5%) patients.[195]

Pulsed dye laser (PDL) PDT

One study evaluated the use of PDL-mediated PDT in the treatment of four HS patients. Three months after the end of the treatment, no lesion improvement was recorded.[196]

PDT combined with surgery

Two studies evaluated the use of 20% ALA PDT combined with surgery in 67 HS patients. The combined therapy was more effective than simple ALA PDT.[197,198]

PDT as a third line treatment in patients with mild-to-moderate HS			
Strength		**Agreement**	
↔	May be considered	Strong consensus	31/31 (100%)

Botulinum toxin B

A small-scale phase II double-blind RCT in 20 HS patients allocated to intralesional injection of botulinum toxin B or placebo for 3 months followed by an open-label treatment has shown a significant DLQI improvement.[199]

Botulinum toxin B as a third line treatment in patients with mild HS			
Strength		**Agreement**	
↔	May be considered	Majority agreement	18/31 (58%)

Metformin

There is inconclusive evidence for the clinical benefit of metformin. No RCT exists. A retrospective series of 53 patients reported an improvement in quality of life and a subjective improvement in 68% of patients.[200] A case

series of 25 patients reported improvement in Sartorius score and DLQI.[201] Metformin may be effective in patients with Insulin resistance which is a comorbidity of hidradenitis suppurativa may also be improved by metformin. In a similar fashion, PCOS which is also more common in patients with HS may also benefit from metformin treatment.

Metformin as a third line treatment in patients with mild-to-moderate HS			
Strength		**Agreement**	
↔	May be considered	Majority agreement	22/31 (71%)

Complement inhibition

Circulating concentrations of the complement split product C5a are increased in HS; surprisingly, plasma concentrations of patients with Hurley III stage lesions are higher than patients with Hurley I stage lesions implying a phenomenon of tissue deposition.[202] A small-scale study in 12 patients refractory to anti-TNF treatment showed substantial clinical efficacy with most of benefit related to the decrease in the count of draining tunnels.[203]

Complement inhibitor(s) as a third line treatment in patients with mild-to-moderate HS			
Strength		**Agreement**	
↔	May be considered	Consensus	24/31 (77%)

SURGERY

Within the chronic inflammatory skin diseases, HS is characterized by a disease progression with a shift from inflammatory skin lesions to irreversible tissue destruction, which is no longer adequately responding to medical treatment options, due to the presence of biofilms within scars. Therefore, surgery plays an important role within the therapeutic armamentarium, a fact that distinguishes HS from other inflammatory skin diseases, such as psoriasis or atopic dermatitis. Like the stepwise approach of medical treatments, surgery is escalated with higher disease severity and more irreversible tissue damage like tunnels and scarring.

Conventional surgery

In acute abscess formation, incision and drainage are useful options followed by a mandatory medical or further surgical treatment. In more severe disease, a larger removal of damaged tissue is indicated. Several surgical techniques co-exist and are in current use (Table 3).[204–209]

Until today, no clear definitions exist in regard to surgical termini like local, wide or radical excision. The general surgical concept however consists of removing the complete irreversibly damaged tissue. Frequently, there is a need of combining surgery with systemic anti-inflammatory treatments, to achieve the highest possible efficacy in patients with Hurley stages II and III.

TABLE 3 Surgical techniques in HS.

Technique	Number of treated patients or meta-analysis studies	Recurrence rate (%)	Follow-up period	References
Deroofing	44 patients	17	Median 3 years	[204]
CO_2-LASER evaporation	58 patients	29	1 year	[205]
CO_2-LASER excision	61 patients	1.1	1 to 19 years	[206]
Wide excision	63 patients	24	5 years	[207]
	97 studies	5	Median 2 years	[208]
	33 studies	8	Mean 3 years	[209]

Incision and drainage in the presence of an acute abscess			
Strength		**Agreement**	
↑↑	Should be recommended	Consensus	25/31 (81%)

Surgical treatment for localized and solitary draining tunnels			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

Wide excision in Hurley II-III where extensive tunnel forming and/or extensive scars are present			
Strength		**Agreement**	
↑↑	Should be recommended	Consensus	29/31 (94%)

Wide excision by surgeons with experience in HS surgery			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

In certain anatomical regions as genital or gluteal regions a multidisciplinary surgery			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

Post-surgical conventional surgery healing

It is difficult to compare surgical and post-surgical treatment modalities for HS because of the complex nature of the disease, the numerous complicated surgical interventions used for treatment and the variable results reported in the literature.

Post-surgical secondary intention healing (SIH)

Excision of the affected skin and closure by SIH—without reconstruction—is a standard option after HS surgery. In a meta-analysis, most patients (37%) received SIH after wide excision.[209] The main drawback of the technique is its lengthiness due to prolonged healing. Depending on the size of the defect, it may be followed by skin grafting to avoid extreme scar contraction. In a recent large study, a 24% recurrence rate was found in a follow-up period of 5 years after wide excision with SIH[208] and a meta-analysis reported a 12%–19% recurrence rate after SIH.[209]

Post-surgical secondary intention healing after surgery of HS			
Strength		**Agreement**	
↑↑	Should be recommended	Consensus	29/31 (94%)

Post-surgical primary closure

Less extensive defects and certain anatomical situations allow primary closure. Surgeons with experience in HS surgery rarely use primary closure after wide excision. Nevertheless, published data show comparable recurrence rates to SIH.[209–211] Delayed primary closure led to a 39% recurrence rate.[212] In this study, patients receiving combined biologic and surgical therapy showed a significantly lower recurrence rate after delayed primary closure (19%).

Post-surgical primary closure in HS			
Strength		**Agreement**	
↓	Is not recommended	Strong consensus	31/31 (100%)

Post-surgical primary closure in certain anatomical regions or for partial closure			
Strength		**Agreement**	
↑	Could be recommended	Strong consensus	31/31 (100%)

Post-surgical reconstruction with immediate or delayed skin grafting

Split thickness skin graft (STSG) coverage of the exposed area either immediately or in a delayed fashion (10–14 days later) is a widely accepted method. Delayed skin grafting is preferentially used in most HS centres. In a study comparing STSG with flaps, all STSG patients ($n = 15$) had normal ranges of motion after bilateral wide excision of axillary HS 6 months after STSG.[213]

Immediate or delayed skin grafting after HS surgery depending on the size of the wound and in specific anatomic areas			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

Post-surgical reconstruction with skin grafting and negative pressure wound treatment (NPWT)

Wide surgical excision and skin grafting complemented with negative pressure wound therapy is reported to be effective, providing a quick healing with little functional impairment in retrospective cohort studies and case series.[214–218]

Following wide surgical excision, skin grafting complemented with negative pressure wound therapy			
Strength		**Agreement**	
↑	Could be recommended	Consensus	25/31 (81%)

Post-surgical reconstruction with flap-plasty

A review analysing articles published between 1990 and 2015 found a flap recurrence rate of 8%,[211] whereas a systematic review and meta-analysis, including studies published between 2004 and 2019 with follow-up periods greater than 1 year reported six studies of flap repair with a pooled recurrence rate of 0% (95% CI 0%–4%).[209] This apparent improvement in post-surgical HS recurrence could be the result of advances in surgery. Previous and parallel medical HS treatment could also have contributed to lower recurrence rates.

Following wide excision, reconstruction with flap plasty			
Strength		**Agreement**	
↔	May be considered	Strong consensus	31/31 (100%)

Deroofing

Deroofing, sometimes called unroofing, is a limited surgical intervention in HS, where only the roof of the tunnels is removed leaving behind the epithelized floor of the tunnels. Unfortunately, the term is heterogeneously used by clinicians for describing also limited excision under local anaesthesia. There is limited evidence on prospective data of deroofing in HS. Most data are based on retrospective case series. The deroofing technique is an effective and fast surgical technique can be easily performed under local anaesthesia, and therefore, it is suitable as an office-based surgical procedure preferably in Hurley stage II.[219] With limited surgery and maximal preservation of the surrounding healthy tissue, painful recurrent lesions are converted into cosmetically acceptable scars, with few postoperative complications.[219,220]

One hundred and four patients with 183 lesions treated with deroofing in three prospective studies showed a combined recurrence rate of 14.7%.[204,221,222] In a retrospective study, 482 operations (363 primary operations and 119 re-operations) using skin-tissue-saving excision with electrosurgical peeling (STEEP) technique under general anaesthesia were assessed.[223] Relapses due to non-radical surgery occurred in 29% of the 363 primary operations and women had significantly higher relapse rates than men.

For the treatment of single tunnels deroofing			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

Carbon dioxide LASER therapy

Scanner assisted carbon dioxide LASER treatment aims at focal complete vaporization of all AN and tunnels, leaving healthy tissues in between the pathological lesions. This implicates that the technique is suitable for Hurley stages I and II and usually not for extensively involved areas. The lesions are vaporized from 'inside and out' until surrounding healthy tissues are reached, superficially and in depth, like deroofing with LASER. In this way, the technique can be tissue sparing and at the same time radical. If used for tunnels, meticulous inspection of remaining parts of tracts is mandatory, like in classical deroofing with cold steel or scissors. Carbon dioxide LASER can also be used to excise restricted skin areas 'en-bloc' with or without LASER coagulation of remnants (marsupialization) in the deep tissues, with less bleeding and therefore better visualization than in standard excisions.[206,224] The postoperative wound bed is usually left for healing by secondary intention, after covering with dressings or use of negative pressure therapy devices.[205,206,224–228] There are several retrospective studies and case series demonstrating a favourable outcome of carbon dioxide LASER treatment, with a low recurrence rate.[43,205,206,224,226–229]

For surgical treatment of HS carbon dioxide LASER			
Strength		**Agreement**	
↔	May be considered	Strong consensus	31/31 (100%)

Energy-based therapies directed against the hair follicle

Based on the assumption that the hair follicle plays an important role in HS pathogenesis, LASERs and intense pulse light (IPL) devices designed for hair removal have been studied in HS. The efficacy of hair removal devices is based on the principle of selective photothermolysis, in which thermally mediated radiation damage is confined to targets at the hair follicles.[230]

Neodymium-doped yttrium aluminium garnet (Nd:YAG) LASER therapy

The Nd:YAG LASER (1064 nm) can facilitate depilation and has been used for treatment of HS.[31,231–233] The idea to use depilation in order to control HS, especially the development of new lesions, in light of the pathogenesis, seems plausible. However, the number of studies is scarce and not of high quality.

IPL therapy

IPL is a frequently used method for hair removal, but it is also used to treat inflammatory lesions in acne or rosacea.[234,235] IPL treatment may be considered to prevent disease progression or ameliorate the disease. Further studies are needed to establish the role of IPL treatment in HS.

Hair removal in typical HS areas by light sources (LASER, IPL)			
Strength		**Agreement**	
↔	May be considered	Consensus	26/34 (76%)

Diode and alexandrite LASER treatment

Only a few case reports case or series have investigated the use of diode- and alexandrite LASERs for HS.[236,237] Treatment with diode- and alexandrite LASERs suggests improvement in HS activity, but evidence is limited based on studies with small sample sizes and inconsistent reporting scales.

1024 nm diode LASER and alexandrite LASER treatment to prevent disease progression or ameliorate the disease			
Strength		**Agreement**	
↔	May be considered	Strong consensus	31/31 (100%)

COMBINATION TREATMENTS (MEDICAL/MEDICAL, MEDICAL/SURGICAL)

HS is an extremely difficult to treat chronic inflammatory disease. Current monotherapies do not often provide satisfying clinical results. This could be explained by a higher inflammatory load compared with other skin diseases, and/or the not yet fully understood complex multi-pathway disease pathogenesis. Regarding the above-mentioned points, a combined treatment targeting multiple inflammatory pathways or multiple pathogenic axes could be a promising approach to achieve better clinical results. However, no prospective studies on the efficacy of pharmaceutical combinations compared with monotherapy for HS have been conducted yet.

Despite the lack of prospective trials, the PIONEER adalimumab trials might suggest that adalimumab in combination with a tetracycline group antibiotic could be slightly more efficient than adalimumab alone (see chapter 'Adalimumab').[10] Furthermore, in a small retrospective study the combination of colchicine with doxycycline showed tendency to higher efficacy compared with colchicine alone (see chapter 'Colchicine').[94] Yet, another retrospective case series showed favourable results for the combination therapy of zinc gluconate and topical triclosan for Hurley stage I disease (see chapter 'Zinc gluconate').[30]

Since we continue to struggle to achieve satisfying results in this complicated multifactorial disease, the possibility of combining pharmaceutical therapies (different inflammatory pathways, bacterial or follicular plugging) should be further explored.

Anakinra and other biologic agents, particularly infliximab and adalimumab, secukinumab, ustekinumab and tildrakizumab have been used, usually achieving incomplete control both of HS and associated conditions.[238–241] Combination of infliximab, classical immunosuppressants, like cyclosporine and immunomodulating agents, such as dapsone, has also been tried, obtaining substantially similar results.[242]

Acitretin may be combined with macrolides to widen the treatment indication and accelerate the therapeutic result. The combination of acitretin 0.44 mg/kg/day and azithromycin 500 mg/day for 3 consecutive days for 4 weeks resulted in significant reduction of IHS4 (8.1 ± 2.9 to 4.6 ± 2.6), pain VAS (6.0 ± 1.95 to 2.1 ± 1.39) and DLQI (16 ± 5.7 to 4.4 ± 3.0) after 8 weeks of treatment in 15 patients.[243]

Combinations of biologics, of biologics with conventional immunosuppressants/immunomodulating agents, or of biologics with antibiotics in classical treatment-resistant HS cases not responding to monotherapy with the above-mentioned agents

Strength		Agreement	
↔	May be considered	Strong consensus	29/29 (100%)

Combining surgery with medical treatments

Surgery and systemic medical treatments have different but complementary purposes: effective in eliminating HS lesions (ideally) definitively, surgery remains a local treatment, whereas systemic medical treatments aim at a global control of the inflammation, without ensuring a complete and definitive control, especially when they are stopped. Their association is therefore logical (both controlling the whole disease and locally getting rid of one or more particularly persistent or disabling lesions), but there is a clear lack of high-quality studies on this specific subject. Additionally, comparison of studies containing surgical procedures are often biased, as internationally accepted definitions of surgical techniques and outcome measures such as recurrence are frequently missing.

There is little documentation on the combination of surgery and antibiotics. Provided that the contraindications and spectrums of action are respected, there is no reason to believe that the combination of antibiotics and surgery, which is usual in many medical and surgical activities, poses any concerns about postoperative complications. Only ertapenem (1 g/day i.v. for 1 to 18 weeks) has been specifically described as a rapid and effective way to improve symptoms in severe forms of HS and proposed as a bridge to surgery (in the absence of *Pseudomonas* against which it is not active).[57,58]

The combination of biologics and surgery is a little bit more debated, mostly because of the expectation that biologics could be used as a drug preparation for surgery. The theoretical goals are then, through (intuitively appropriate) preoperative control of inflammation, to (1) reduce indications for surgery, (2) limit the extent of surgery and (3) improve surgical outcomes (reduce the local recurrence rate). There is only limited data in the literature to suggest that the theoretic third objective may be achieved by perioperative biologics.[13,212,244–247] In a comparison of 21 patients undergoing combined surgery and then biologic therapy versus surgery alone, the combination showed lower rates of recurrence/disease progression (19% vs. 38.5% for surgery alone; $p < 0.01$). New disease developed in 18% and 50% of combined treatments and surgery-only groups, respectively. The disease-free interval was also higher in the combination group (18.5 vs. 6 months; $p < 0.001$).[212]

Combination with surgery is well supported by a phase 4, randomized, double-blind RCT of adalimumab in conjunction with surgery.[13] Two hundred and six patients with moderate-to-severe HS requiring radical surgery (Hurley stage III) in an axillary or inguinal region and two other anatomical regions affected were randomized 1:1 to receive adalimumab 40 mg s.c. once weekly or placebo during presurgery (12 weeks), perioperative (2 weeks) and postoperative (10 weeks) periods. At Week 12, 49/103 (48%) patients receiving adalimumab versus 35/103 (34%) under placebo ($p = 0.049$) achieved HiSCR across all body regions. No increased risk of postoperative wound infection after wide-excision surgery followed by secondary intention healing, complications or haemorrhage was observed with adalimumab versus placebo.[238–241] Antibiotics may be continued during biologic therapy.

Reciprocally, adding surgery to biologics is expected as a mean to increase the ability of biologics to control HS. A retrospective case series ($n = 30$; HS Hurley stage II or III) evaluated patients undergoing treatment with infliximab and then surgery (in 24 of the 30 patients; deroofing, small/large incisions) to remove remaining tunnels.[248] At 50 months, 37% of patients treated with infliximab + adjuvant surgery were disease-free versus 13% of patients treated with infliximab alone. In a longitudinal observational study ($n = 68$), the impact of surgical intervention with adjunctive biologic therapy was evaluated.[249] The effect of biologics was greater in patients who also underwent surgery ($p = 0.013$). However, timing of biologics relative to surgery did not impact efficacy. Patients who received HS surgery with biologic therapy were most likely to achieve a 75% reduction in inflammatory AN ($p = 0.017$). The only randomized controlled study on the administration of adalimumab in conjunction with surgery (wide excision and secondary intention healing) in moderate-to-severe HS failed to show a reduction in surgery indications and extent.[13] It however clearly demonstrated that is was safe to combine adalimumab with surgery. The action of biologics on wound healing is not explored to date.

Continuation of adalimumab treatment during surgery			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

TREATMENT OF DRAINING TUNNELS

Draining tunnels is the most bothersome physical HS sign for the patients and their treatment is still a clinical challenge. When multiple draining tunnels are present, an effort to reduce the inflammatory component with anti-inflammatory treatment before surgery is advisable and well supported by the evidence. For adalimumab, it is well supported by high-quality evidence from a phase 4, double-blind RCT of adalimumab in conjunction with surgery.[13] No increased risk of postoperative wound infection, complication or haemorrhage was observed with adalimumab versus placebo. The use of medical therapy prior to surgical intervention can achieve control of inflammation. Bimekizumab,[12] secukinumab[11] and spesolimab[145] have been shown in RCTs to reduce the number of draining tunnels.

After anti-inflammatory treatment or when only solitary draining tunnels are present, surgical approaches			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

The use medical therapy prior to surgical intervention in order to achieve control of inflammation			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

WOUND CARE

General measures

Draining tunnels and rupture of abscesses with discharge of malodorous pus negatively impact quality of life in HS.[250] Appropriate wound care is an important domain of HS management as it improves patients' quality of life.[251] Most recommendations are based on general wound care guidelines and expert opinion. In chronic wound care, the choice of dressing is based on the affected body region, the absorption capacity, the sufficient adherence of the dressing and the fixation material.[250] Usually, the most suitable wound dressings are superabsorbent foams alone or in combination with alginates, atraumatic adhesives such as silicone and nonadherent dressings (Table 4).

In postoperative wound care, there is a lack of evidence on wound care strategies. Current knowledge is based on observational studies and case series.[223,252] Postoperative wound care in HS is dependent on the closure techniques, whether primary or secondary closure, skin grafting or transposition flap and on the anatomical region of the intervention.[253]

TABLE 4 Factors affect the choice of wound dressing.

- Extent of involvement
- Morphology of the lesions
- Volume of exudate
- Cost of the product
- Availability of the dressing
- Location of the lesion
- Any need for antimicrobials

Local surgical guidelines and wound care are mostly followed.[253,254] Relatively large postoperative wounds producing higher volumes of exudate may benefit from negative pressure wound therapy.

Negative pressure therapy

Relatively large postoperative wounds producing higher volumes of exudate may benefit from negative pressure wound therapy. A wound care plan is recommended in the management of patients with HS chronic or postoperative wounds. The plan should be personalized taking into account anatomical location, relapsing draining tunnels, spontaneously rupturing abscesses, volume of exudate, dressing availability and patient preference. It is advisable to take into account different factors at the prescription of wound dressings, including the frequency of wound dressing changes, the flexibility of the wound dressing, the absorbent capacity and the size of the affected region.

Involvement of an expert on HS wounds in the case of severe chronic HS suppurative lesions			
Strength		**Agreement**	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

LIFESTYLE INTERVENTIONS

Weight management

Obesity is strongly associated with HS, with a systematic review confirming an odds ratio of 3.45 (95% CI 2.20–5.38) for the association.[255] A BMI has been linked to greater disease severity[256] and a BMI increase of one unit was associated with a 0.84 unit increase in mean Sartorius severity score.[257] There is no RCT to confirm whether weight reduction in obese HS patients reduces disease severity. In a retrospective case series of 12 patients, substantial weight loss from bariatric surgery improved HS relative to a control group.[258] In some cases, residual excess skin folds may cause ongoing skin problems. While the evidence regarding weight reduction in obese HS patients remains equivocal, it is advisable because of the general health benefits and potential improvement of HS-associated conditions such as type 2

diabetes, hypertension, metabolic syndrome, dyslipidaemia and cardiovascular disease.[259] Regular physical activity may help in maintaining or losing weight, as well as improving the metabolic alterations associated with obesity. The development of glucagon-like peptide analogues, which are approved by the EMA for the treatment of obesity, may have important implications for HS treatment. One retrospective study of the adjunctive use of semaglutide in HS patients showed a beneficial reduction in HS flares and an improvement in quality of life.[182]

Smoking cessation

Tobacco smoking is consistently associated with HS, a systematic review finding an odds ratio of 4.34 (95% CI, 2.48–7.60) for the association with current smoking.[255] There is some evidence to suggest a dose–response with greater smoking pack years linked to more severe HS.[256] However, an increase in disease recurrence following surgery for HS in current smokers has not been demonstrated in most studies.[259] Similarly to weight reduction, there is no RCT providing evidence of the effect of smoking cessation on HS severity. Nevertheless, the overall health benefits of smoking cessation, particularly in the context of the higher risk of cardiovascular disease associated with HS, means that smoking cessation, where relevant, is advisable.

Dietary modification

Dietary modification and supplements have been investigated in a few small studies; however, the evidence is insufficient to make a specific recommendation beyond maintaining a healthy weight. A prospective cohort study followed 12 patients undergoing surgery for HS who adhered to a diet free from Brewer's yeast for 12 months; however, the effects of the diet cannot be distinguished from the effects of surgery, and there was no control group.[260] Dairy-free or dairy-restricted diets have been investigated in an uncontrolled retrospective cohort study and a case series, however the evidence quality is classified as very low.[261] A pilot study found that all 22 HS patients were deficient in vitamin D and supplementation produced improvement in 11/14 individuals after 6 months.[262]

Avoidance of friction

It is likely that the link between obesity and HS is at least partially explained by skin friction, due to an increase in flexural skin folds. An example of the effects of friction is the occurrence of HS-like lesions reported on amputation stumps.[263] Underwears that minimize friction are advised. Anecdotally, exercise-induced HS flares due to friction may confound patient attempts to lose weight.

Weight reduction in overweight patients with HS, particularly because of general health benefits and potential improvement of HS-associated conditions such as type 2 diabetes, hypertension, metabolic syndrome, dyslipidemia, and cardiovascular disease

Strength		Agreement	
↑	Could be recommended	Strong consensus	31/31 (100%)

Cessation of smoking in HS, particularly in the context of the higher risk of cardiovascular disease associated with HS

Strength		Agreement	
↑↑	Should be recommended	Strong consensus	31/31 (100%)

Dietary restrictions, beyond maintenance of healthy weight, in patients with HS

Strength		Agreement	
↓	Are not recommended	Strong consensus	31/31 (100%)

LONG-TERM TREATMENT

Long-term treatment in HS should be considered and defined as more than 6 months. Long-term treatment definition also includes a maintenance phase of treatment (see chapter 'Maintenance treatment'). Long-term continuous treatment with adalimumab (data of at least 2 year of continuous use) maintains a level of sustained effectiveness (on physician signs, pain and quality of life) in responders with an acceptable safety profile.[112]

MAINTENANCE TREATMENT

A maintenance phase of treatment in the dermatological field is usually intended as the one that follows the active phase of treatment when a defined clinical result has been achieved. The aim of the maintenance treatment is to maintain the acquired results and to prevent recurrences of the disease. Regarding the concept of maintenance therapy in HS, no acknowledged and shared definition can be found in the literature. Specific relevant publications do not exist, except for citing the concept of maintenance.

Using PIONEER integrated trial results, the optimal medium-term maintenance dosing strategy for adalimumab in moderate-to-severe HS has been evaluated.[264] Maintenance treatment was defined as a therapy that can be used after achieving remission (achievement of HiSCR at Week 12) in order to prevent progression and flare ups (i.e. HiSCR loss). Adalimumab 40 mg/week, effective throughout 36 weeks, was the optimal maintenance medium-term dosing regimen for this population. After at least partial treatment success with adalimumab weekly short-term therapy (12 weeks), continuing weekly dosing during the subsequent 24 weeks had better outcomes than dose reduction or treatment interruption. Patients who did

not exhibit at least a partial response to weekly adalimumab by Week 12 were unlikely to benefit from continued therapy. In a recently published prospective multicentric study on 107 patients with HS, two different regimens, that is adalimumab 40 mg/week or 80 mg every other week were defined as maintenance treatment, with no statistically significant differences between them in the term of baseline–Week 32 outcomes of the IHS4, DLQI, pain VAS and PGA.[265] In short-term studies, recurrence follow discontinuation of treatment after 11–12 weeks. Long-term (at least 2 years) continuous treatment maintains a level of consistent effectiveness in responders with an acceptable safety profile.[112]

In another recent study, maintenance therapy for 92 mild-to-moderate HS patients after 12 weeks of beneficial treatment with tetracyclines p.o. was proposed with capsules containing 90 mg zinc gluconate and 30 mg nicotinamide once daily for 90 days.[98] Disease-free survival was significantly longer in the treated group (vs. non-treated control group), and it showed sustained improvement even after discontinuation of oral supplementation.

The efficacy of infliximab 7.5 to 10 mg/kg in HS patients has been evaluated in a study.[266] The maintenance treatment every 4 weeks, was started when the outcome goals, referred to HS-PGA, NRS pain and MCIC QoL, were achieved. In this case, a well-defined type of clinical result was considered, but was variable, from full clearance to mildly severe disease still present.

Maintenance of remission after surgery for HS is also an important concept. Combination with surgery is well supported by high-quality evidence from the phase 4, randomized, double-blind, placebo-controlled study of adalimumab in conjunction with surgery.[13] Adalimumab was efficacious in conjunction with wide-excision surgery followed by secondary intention healing, with no need to interrupt treatment prior to surgery. Combination with infliximab after surgery is also a plausible concept but is only based on case series.[267]

Adalimumab 40 mg/week or 80mg/every other week also after surgery for maintenance of remission			
Strength		**Agreement**	
↑	Could be recommended	Strong consensus	31/31 (100%)

Infliximab 7.5 to 10 mg/kg every 4 weeks also after surgery for maintenance of remission			
Strength		**Agreement**	
↔	May be considered	Majority agreement	18/34 (53%)

Zinc gluconate 90 mg/d and nicotinamide 30 mg/d for 90 days for mild-to-moderate HS			
Strength		**Agreement**	
↓	Is not recommended	Consensus	28/31 (90%)

TREATMENT OPTIONS IN CLASSICAL TREATMENT-RESISTANT HS

Loss of response appears to be a frequent concern in the long-term HS treatment with anti-TNF agents.[268] At present, there is a lack of evidence in terms of clinical predictors and/or biomarkers guiding the choice among the different drugs and the decision is mainly based on the presence of comorbid conditions. Similarly, the decision to switch between different drugs is mainly based on lack or loss of response and/or the occurrence of adverse events, including paradoxical reactions.[269] HS patients that either experience inadequate disease control or loss of response with adalimumab 40 mg/week or 80 mg/every other week are defined as classical treatment-resistant HS cases. According to the results of a retrospective case series of 14 patients that had been treated with adalimumab 40 mg/week, temporary administration of intensified adalimumab 80 mg/week treatment resulted in a significant reduction in IHS4 score.[270] In a retrospective study on 22 patients with severe HS, who had experienced loss of response to adalimumab, dose intensification to adalimumab 80 mg/week resulted in the fulfilment of HiSCR in 68% at Week 12. Similarly, in a prospective study, that evaluated variable dose intensification regimens, that is adalimumab 80 mg every 10 or 12 days, in moderate-to-severe HS patients experiencing loss of response, 62% of participants achieved the HiSCR at Week 12.[271]

In patients with inadequate response or loss of satisfactory response to infliximab with time, a dose intensification (7.5–10 mg/kg every 4 weeks) may be administered to improve the therapeutic result.[266] In a retrospective cohort study of 52 HS patients, most of whom had failed to adalimumab, infliximab 10 mg/kg every 6–8 weeks was suggested as the optimal starting dose, with 64% of participants achieving the HiSCR.[272]

Adalimumab temporal dose-intensification in patients with inadequate response or loss of satisfactory response			
Strength		**Agreement**	
↔	May be considered	Majority agreement	19/32 (59%)

Infliximab temporal dose-intensification in patients with inadequate response or loss of satisfactory response			
Strength		**Agreement**	
↔	May be considered	Majority agreement	18/34 (53%)

An open-label cohort study on 10 patients has shown that brodalumab dose intensification (210 mg/week) was efficient in patients with inconsistent disease control, for example cyclical recurrences.[130]

Brodalumab intensification in inconsistent HS control			
Strength		**Agreement**	
↔	May be considered	Strong consensus	29/29 (100%)

Dose or frequency intensified ustekinumab regimens have led to improvements in a series of 6 severe, adalimumab-experienced HS cases.[273]

Ustekinumab intensification in classical treatment-resistant HS patients			
Strength		**Agreement**	
↔	May be considered	Strong consensus	29/29 (100%)

In failure to respond to dose intensified adalimumab, anti-IL-17 or off label anti-IL-12/23 agents with standard psoriasis regimens or intensified dosage, IL-1 inhibitors or JAK inhibitors			
Strength		**Agreement**	
↔	May be considered	Strong consensus	29/29 (100%)

SYNDROMIC HS TREATMENT

Syndromic forms of HS, including pyoderma gangrenosum, acne and suppurative hidradenitis (PASH), pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis (PAPASH), psoriatic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis (PsAPASH), pyoderma gangrenosum, acne, suppurative hidradenitis and ankylosing spondylitis (PASS), and pustular psoriasis, arthritis, pyoderma gangrenosum, synovitis, acne and suppurative hidradenitis (PsAPSASH) represent paradigms of severe, treatment-refractory HS.[274,275] Due to their rarity, evidence on the treatment of these forms is very limited and consists mainly of isolated reports and small case series.

TREATMENT BIOMARKERS

Faecal calprotectin (FC), albeit infrequently used, has been reported as a possible screening tool for underlying IBD in paediatric HS patients,[276] but other authors failed to demonstrate an association between FC levels and comorbid IBD in adult HS patients.[277] Moreover, FC has been suggested as a biomarker of HS disease activity,[278] reducing its value as a screening tool for underlying IBD.

Screening for co-morbid inflammatory bowel disease (IBD), based on accurate history-taking and possible gastroenterological referral in case of gastrointestinal symptoms prior to prescribing medical treatment			
Strength		**Agreement**	
↔	May be considered	Strong consensus	29/29 (100%)

The use of fecal calprotectin as a biomarker for HS or IBD in HS			
Strength		**Agreement**	
↔	May be considered	Strong consensus	29/29 (100%)

MULTIDISCIPLINARY APPROACH

HS patients frequently present clinical patterns that are best addressed by specialists from multiple fields of medicine and surgery. A multidisciplinary approach refers to the coordination and collaboration of health care providers (HCP) with different specializations who work in parallel in order to improve the outcome of the patients.[279] There is no available randomized or non-randomized clinical trial which demonstrates that the availability of a multidisciplinary approach improves the outcome of HS. A study in 49 patients showed that the level of satisfaction is increased by the patients when this multidisciplinary approach is provided in a parallel time.[245] There is no doubt that patients are usually in need of consultation of several specialists for their primary disease, but also for their comorbidities.

THERAPEUTIC CONCLUSIONS AND ALGORITHM

Based on consensual recommendations, the expert group has outlined the following therapeutic algorithm of active inflammatory HS and inactive, predominantly non-inflammatory HS for the stage-related therapy of HS (Figure 1).

PATIENTS VIEW

Recommendations to HS patients

- Identify your most troublesome physical symptoms (such as pain, wound care, odour from wounds and fatigue), any HS-associated problems, factors that may worsen/help, and the best care solutions for these, whether these solutions involve medical treatment, support or others.
- Connect with, talk with, share with and learn from others, that is family, friends, other people with HS, HS groups, other patient groups and your medical team.
- Identify your main needs: disability, emotional, financial, mental, physical, relationships, sexual, social, study/work difficulties and so on.
- Try to identify the most appropriate care (i.e. medical treatments and supports), your training, becoming involved in HS research, sharing your lived experience with your medical team and other HCPs and others who have HS.
- Be kind to yourself and your body. A healthy lifestyle may improve your HS, for example stopping smoking, healthy diet, prioritizing rest, sleep and well-being, managing your stress, fresh air and natural daylight, and if possible, movement or exercise that you enjoy. Ask your medical team and others for help, resources and support if needed.
- An illness diary in conjunction with photographs can help to document the course of the illness. In this way, the doctor(s) can be informed about the course of the disease between medical consultations. This can also be helpful when dealing with the authorities.

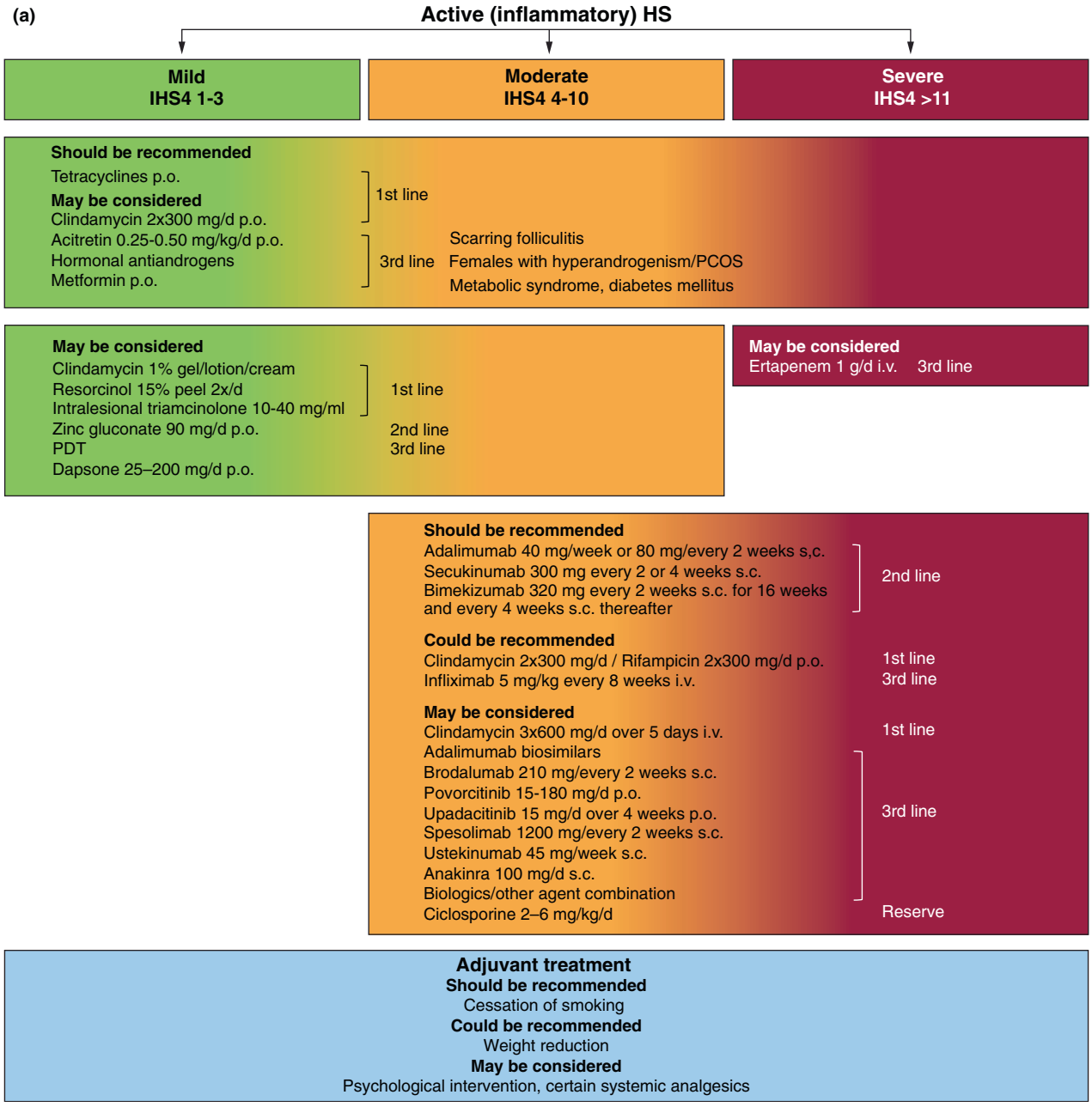

FIGURE 1 HS treatment algorithm. (a) Therapy of active (inflammatory) HS, (b) Therapy of inactive (non-inflammatory) HS. [Correction added on 21 Janaury 2025, after first online publication: Figure 1a has been revised.]

Recommendations to HCP

- Address all the patients' symptoms and difficulties, including but not limited to pain, wound care, odour, fatigue, those related to comorbidities (including mental health support and well-being) and those related to financial and social impairments.
- Watch out for possible superinfections.
- Access to emergency care for patients is vital.
- The first consultation is critical:
  - Use appropriate language and give an honest evaluation of the disease, treatment options and management expectations.
  - Highlight the increase in HS research and the many treatments in development.
  - Mention comorbidities, screening and management of these.
  - Suggestions about lifestyle changes (where appropriate) and any sensitive issues need not to be mentioned on the first visit. Establishing an honest, respectful and trusting relationship is conducive to this.
- Provide information about credible and reputable HS patient groups and associations, directory of HS practitioners, online HS resources and other relevant information.
- Promote patients' and HCP education through dedicated programmes using good instructional design principles

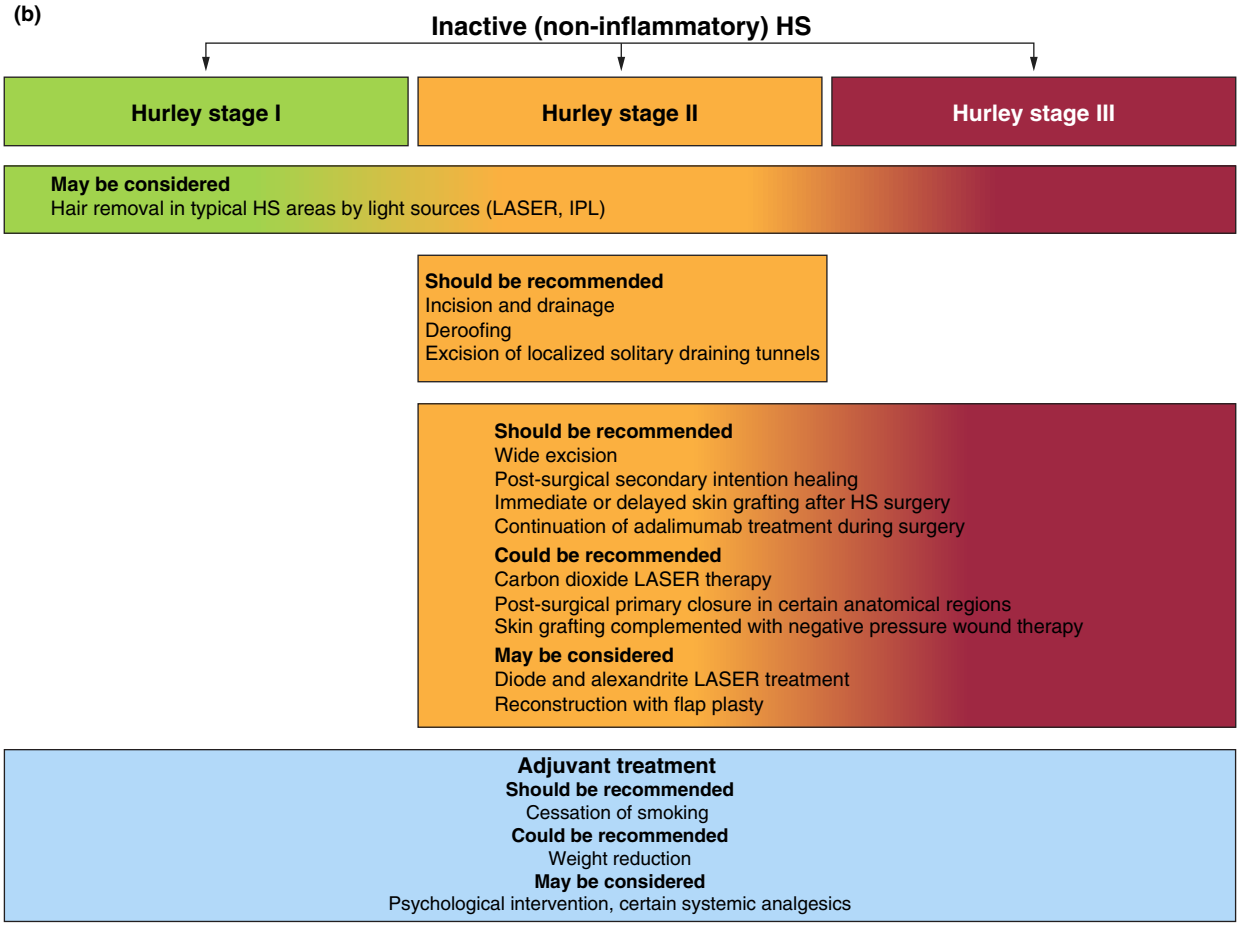

FIGURE 1 (Continued)

and practices. Encourage intrafamilial communication by inviting relatives to consultations, especially the first.
- Support shared decision making, considering the patient's history and their wishes for treatments, surgery, lifestyle adjustments (if needed) and other measures.
- Promote patient involvement in research.
- Collaborate with all the main stakeholders in the care process: medical and paramedical HCP, the patient and their network, patient associations, industry, health authorities, others.

AUTHOR CONTRIBUTIONS

All authors have met the criteria for authorship, having made substantial contributions to the work and taking public responsibility for relevant portions of the content, as follows: *Objectives of the guidelines*, *Objectives of HS treatment*, *What's new?*, *Overview of therapeutic options*: Zouboulis CC. *Scoring system for clinical trials*: Tzellos T, Marzano AV and Molina-Leyva A. *Adjuvant therapy*: Szégedi A, Molina-Leyva A and Horváth B. *Topical therapy—nonantibiotics*: Bukvic Mokos Z, Dolenc-Voljc M and Bechara FG. *Topical antibiotics*: Zouboulis CC, Jemec GBE and Prignano F. *Systemic antibiotics*: Kemény L, van Straalen KR and Saunte DML. *Consideration of bacterial resistance under long-term antibiotic treatment*: Giamarellos-Bourboulis EJ, Saunte and Nassif A. *Anti-inflammatory treatment*: Bukvic Mokos Z, Szégedi A, Prens EP, Zouboulis CC, Jemec GBE, Liakou AI, Dolenc-Voljc M, Valiukeviciene S and Kirby B. *Hormonal treatment of HS*: Bukvic Mokos Z, Prens EP and Szegedi A. *Biologics*: Prens EP, Tzellos T, Kirby B and Zouboulis CC. *Eligibility for biologics and advanced molecules*: Kirby B, Molina-Leyva A and Hunger RE. *Retinoids*: Zouboulis CC, Jemec GBE and Matusiak Ł. *Analgesics*: Nassif A, Ioannidis D, Podda M and Tzellos T. *Experimental therapies*: Prignano F, Kirby B and Giamarellos-Bourboulis EJ. *Surgery*: Podda M, Guillem P, Bechara FG, Grimstad Ø, Horváth B, Hunger RE and Kemény L. van der Zee HH. *Combination treatments (medical/medical, medical/surgical)*: Guillem P, van der Zee HH and Bechara FG. *Treatment of draining tunnels*: Tzellos T, Bechara FG and Grimstad Ø. *Wound care*: Horváth B, Hunger RE, Ingram JR and Romanelli M. *Lifestyle interventions*: Ingram JR, Horváth B and Dolenc-Voljc M. *Long-term treatment*: Horváth B, Ioannidis D, Jemec GBE and Tzellos T. *Maintenance treatment*: Matusiak Ł, Ioannidis D, Bettoli V and Tzellos T.

Treatment options in classical treatment-resistant HS: Ioannidis D, Zouboulis CC, Marzano AV and Tzellos T. *Syndromic HS treatment*, *Treatment biomarkers*: Marzano AV and Zouboulis CC. *Multidisciplinary approach*: Bettoli V, Giamarellos-Bourboulis EJ and Guillem P. *Therapeutic conclusions and algorithm*: Zouboulis CC, Jemec GBE and Prens EP. *Patients view*: McGrath B, Raynal H, Villumsen B and Just E. C.C. Zouboulis takes overall responsibility for the integrity of the entire work, from inception to the published article. All authors have participated at the guidelines preparation and voting procedure, drafted and critically revising the article for important intellectual content and finally approved the version to be published.

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CONFLICT OF INTEREST STATEMENT

CCZ has received advisory board and consultancy fees from Almirall, Boehringer Ingelheim, Eli Lilly, Idorsia, Incyte, L'OREAL, MSD, NAOS-BIODERMA, Novartis, Pfizer, PPM, Sanofi and UCB, and lecture honoraria from Almirall, Amgen, Biogen, Novartis, Pfizer and UCB. His departments have received grants from Astra Zeneca, Boehringer Ingelheim, the Brandenburg Medical School Theodor Fontane, the EADV, the European Union, the German Federal Ministry of Education and Research, GSK, Inflarx, MSD, Novartis, Relaxera and UCB for his participation as clinical and research investigator. He is the president of the EHSF e.V., coordinator of the ALLOCATE Skin group of the

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DATA AVAILABILITY STATEMENT

The data that support the findings of this guideline are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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