Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-179 Secukinumab

Stand: Oktober 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Secukinumab
[mittelschwere bis schwere aktive Hidradenitis suppurativa]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	siehe unter II.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Chirurgische Interventionen
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Secukinumab	Geplantes Anwendungsgebiet laut Beratungsanforderung: **Secukinumab ist indiziert zur Behandlung der mittelschweren bis schweren Hidradenitis suppurativa (HS) bei Erwachsenen, die unzureichend auf eine konventionelle systemische HS-Therapie ansprechen.**
Adalimumab ATC: L04AB04 Humira®	<u>Hidradenitis suppurativa (Acne inversa)</u> Humira ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Hidradenitis suppurativa (HS) bei Erwachsenen und Jugendlichen ab einem Alter von 12 Jahren, die unzureichend auf eine konventionelle systemische HS-Therapie ansprechen.
Clindamycin ATC: J01FF01 Clindamycin-ratiopharm® 600 mg Filmtabletten	Clindamycin wird bei Infektionen angewendet, die durch Clindamycin-empfindliche Bakterien verursacht werden, wie - […] - Schwer behandelbare Infektionen der Haut und Weichteile wie Akne, Furunkulose, Cellulitis, Impetigo, Abszesse, Wundinfektionen, Erysipel und Nagelfalzinfektionen. - […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-179 (Secukinumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. August 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse effects
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

zur Behandlung der mittelschweren bis schweren Hidradenitis suppurativa (HS) bei Erwachsenen, die unzureichend auf eine konventionelle systemische HS-Therapie ansprechen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation: *Hidradenitis suppurativa* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 03.04.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 77 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 7 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten G-BA Beschlüsse/IQWiG Berichte identifiziert.

3.2 Cochrane Reviews

Ingram et al., 2015 [3].

Interventions for hidradenitis suppurativa

Fragestellung

To assess the effects of interventions for HS in people of all ages.

Methodik

Population:

- All individuals of either sex and any age and ethnicity with a clinical diagnosis of HS made by a medical practitioner. Ideally, the clinical diagnosis conformed to the consensus disease definition.

Intervention/Komparator

- The broad scope of this review meant that we included all interventions provided that they were assessed by at least one RCT. Preliminary literature searches indicated that over 40 interventions have been used for HS, although many lack RCT evidence. In order to structure the review, we grouped interventions into three categories, namely, pharmacological, surgical, and other interventions (siehe Ergebnisteil).

Endpunkte:

- Primary outcomes: Quality of life, Adverse effects (AEs)
- Secondary outcomes: Participant global self-assessment, Pain score, Hidradenitis Severity Score, Physician Global Assessment, Duration of remission, measured by the number of days until first new lesion or disease flare

Recherche/Suchzeitraum:

- up to 13 August 2015

Qualitätsbewertung der Studien:

- Cochrane Approach /GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Twelve trials, with 615 participants
- A single RCT that was underpowered to detect clinically meaningful differences investigated most interventions.
- There were four trials of anti-TNF-(tumour necrosis factor-alpha) therapies, which included etanercept, infliximab, and adalimumab.

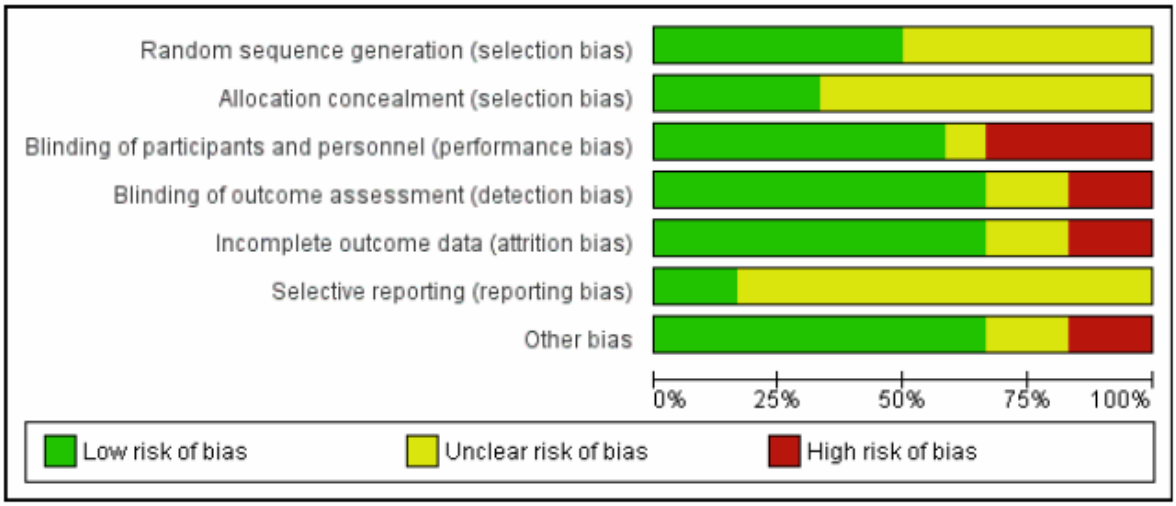
Charakteristika der Population:

- All studies involved adults aged 18 years and over with a clinical diagnosis of hidradenitis suppurativa (HS)

- Six studies required baseline HS severity to be moderate to severe. One study required baseline HS severity to be mild to moderate (stage I to II). Of the remaining five trials, three required 'active' disease, one permitted a range from mild to severe HS, and one did not stipulate a specific disease severity but required a HS disease duration of at least six months

Qualität der Studien:

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'risk of bias' item presented as percentages across all included studies.



Studienergebnisse:

- Adalimumab 40 mg weekly improved the Dermatology Life Quality Index (DLQI) score in participants with moderate to severe HS by 4.0 points relative to placebo (95% confidence interval (CI) -6.5 to -1.5 points), an effect size approximately equal to the DLQI minimal clinically important difference. We reduced the evidence quality to 'moderate' because the effect size was based on the results of only one study.
- In a meta-analysis of two studies with 124 participants, standard dose adalimumab 40 mg every other week was ineffective compared with placebo (moderate quality evidence).
- In a smaller study of 38 participants, of whom only 33 provided efficacy data, infliximab 5 mg/kg treatment improved DLQI by 8.4 DLQI points after eight weeks.
- Etanercept 50 mg twice weekly was well tolerated but ineffective.
- In a RCT of 200 participants, no difference was found in surgical complications (moderate quality evidence) or risk of recurrence (moderate quality evidence) in those randomised to receive a gentamicin-collagen sponge prior to primary closure compared with primary closure alone.
- RCTs of other interventions, including topical clindamycin 1% solution; oral tetracycline; oral ethinylestradiol 50 mcg with either cyproterone acetate 50 mg or norgestrel 500 mcg; intense pulsed light; neodymium-doped yttrium aluminium garnet (Nd:YAG) laser; methylene blue gel photodynamic therapy; and staphage lysate, were relatively small studies, preventing firm conclusions due to imprecision.

Anmerkung/Fazit der Autoren

Many knowledge gaps exist in RCT evidence for HS. Moderate quality evidence exists for adalimumab, which improves DLQI score when 40 mg is given weekly, twice the standard psoriasis dose. However, the 95% confidence interval includes an effect size of only 1.5 DLQI points, which may not be clinically relevant, and the safety profile of weekly dosing has not been fully established. Infliximab also improves quality of life, based on moderate quality evidence.

More RCTs are needed in most areas of HS care, particularly oral treatments and the type and timing of surgical procedures. Outcomes should be validated, ideally, including a minimal clinically important difference for HS.

Kommentare zum Review

- Siehe auch Ingram et al. 2016 [4]

3.3 Systematische Reviews

Tchero et al., 2019 [6].

Hidradenitis suppurativa: a systematic review and meta‐analysis of therapeutic interventions.

Fragestellung

To investigate the safety and efficacy of available treatment options (medical, radiation and surgical) for hidradenitis suppurativa with published data in the literature.

Methodik

Population:

- Patients with hidradenitis suppurativa

Intervention:

- Hidradenitis suppurativa treatments including antibiotics, tumor necrosis factor‐ α

Komparator:

- placebo or another active agent

Endpunkte:

- Siehe Ergebnisteil

Recherche/Suchzeitraum:

- on January 26, 2018

Qualitätsbewertung der Studien:

- 5‐point JADAD scale / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 randomized trials

Qualität der Studien:

- Regarding quality assessment, except for four studies, all the trials were of high quality.

Studienergebnisse:

- Adalimumab, an anti‐tumor necrosis factor antibody, was superior to placebo in reducing Sartorius score (standardized mean difference = −0.32, confidence interval [−0.46, −0.18], P < 0.0001) and pain (risk ratio = 1.42, confidence interval [1.07, 1.9], P = 0.02), when given weekly (not every other week).
- Combination therapies (such as antibiotics and hyperbaric oxygen therapy) have been tested, which have shown promising results that are yet to be confirmed. Based on the quality of evidence, the most recommended treatments for hidradenitis suppurativa include adalimumab and laser therapy.

- Surgery (either by simple excision or complete local excision followed by skin graft) is the first choice for intractable disease presenting in the late stages. However, the evidence on most of these treatments is deficient and further randomized trials are needed to establish the most efficient therapies for hidradenitis suppurativa management.

Table 2: Strength of recommendation of the therapies for hidradenitis suppurativa based on the quality of evidence

Strength of recommendation	Therapy (quality of evidence, line of therapy)
A	Adalimumab, systemic (Ib, first line) Flap plasty reconstruction (Ia/IIa, surgery) Laser therapy, CO_2 or Nd:YAG (Ib, surgery)
B	Tetracycline, oral (IIb, first line) Total excision, lesion and surrounding skin with hair follicles (IIb, surgery) Second intention healing (IIb, surgery) Infliximab, systemic (Ib, second line)
C	Clindamycin, oral (III, first line) Individual lesion excision/curettage (III, surgery) Primary closure/skin graft (III, surgery) Zinc gluconate/resorcinol (III, second line) Acitretin/etretinate (III, second line)
D	Deroofing (IV, surgery) Intense pulsed light (IV, surgery) Corticosteroid, intralesional/systemic (IV, second line) Colchicine/botulinum toxin/isotretinoin/dapsone/cyclosporine/hormones (IV, third line)

Ia (A): Meta-analysis of RCT, Ib (A): RCT, IIa (B): Controlled nonrandomized study, IIb (B): Quasi-experimental study, III (C): Nonexperimental studies (case-control studies, correlation, comparative studies), IV (D): Expert committee reports. RCT: Randomized clinical trials, Nd: YAG: Neodymium-doped yttrium aluminum garnet

Anmerkung/Fazit der Autoren

In this review, we presented an evidence‐based evaluation of hidradenitis suppurativa management modalities. Further, we prepared a treatment algorithm based on the evidence and our own experience at our clinic. Owing to the complex nature of hidradenitis suppurativa, the patient will have a better chance of recovery if diagnosed at early stage, followed by proper treatment, preferably based on staging followed by adherence to evidence‐based algorithm. All patients may need one or more of adjuvant therapies to manage associated pain, depression, weight loss and infections. (…)

Mehdizadeh et al., 2015 [5].

Recurrence of hidradenitis suppurativa after surgical management: a systematic review and meta-analysis.

Fragestellung

This study provides a comprehensive systematic review of surgical approaches in the management of HS.

Methodik

Population:

- patients with HS

Intervention/Komparator:

- Surgical approaches include incision and drainage, deroofing, and local and wide excision. Options for healing after wide surgical excision include primary closure, secondary intention wound healing, skin grafting, and skin flaps.

Endpunkte:

- Recurrences

Recherche/Suchzeitraum:

- between 1990 and the end of March 2015. Studies were systematically searched in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL)

Qualitätsbewertung der Studien:

- k.A.

Ergebnisse

Anzahl eingeschlossener Studien:

- 22 articles

Qualität der Studien:

- poor quality evidence

Studienergebnisse:

- The estimated average recurrences were:
  - wide excision, 13.0% (95% confidence interval [CI], 5.0-22.0%);
  - local incision, 22.0% (95% CI, 10.0-37.0%); and
  - deroofing, 27.0% (95% CI, 23.0-31.0%).
- In the wide excision group, recurrence rates were as follows:
  - 15% (95% CI, 0-72%) for primary closure,
  - 8% (95% CI, 2.0-16.0%) for using flaps, and
  - 6.0% (95% CI, 0.0-24.0%) for grafting.
- The secondary intention healing option was most commonly chosen after local excision and deroofing.

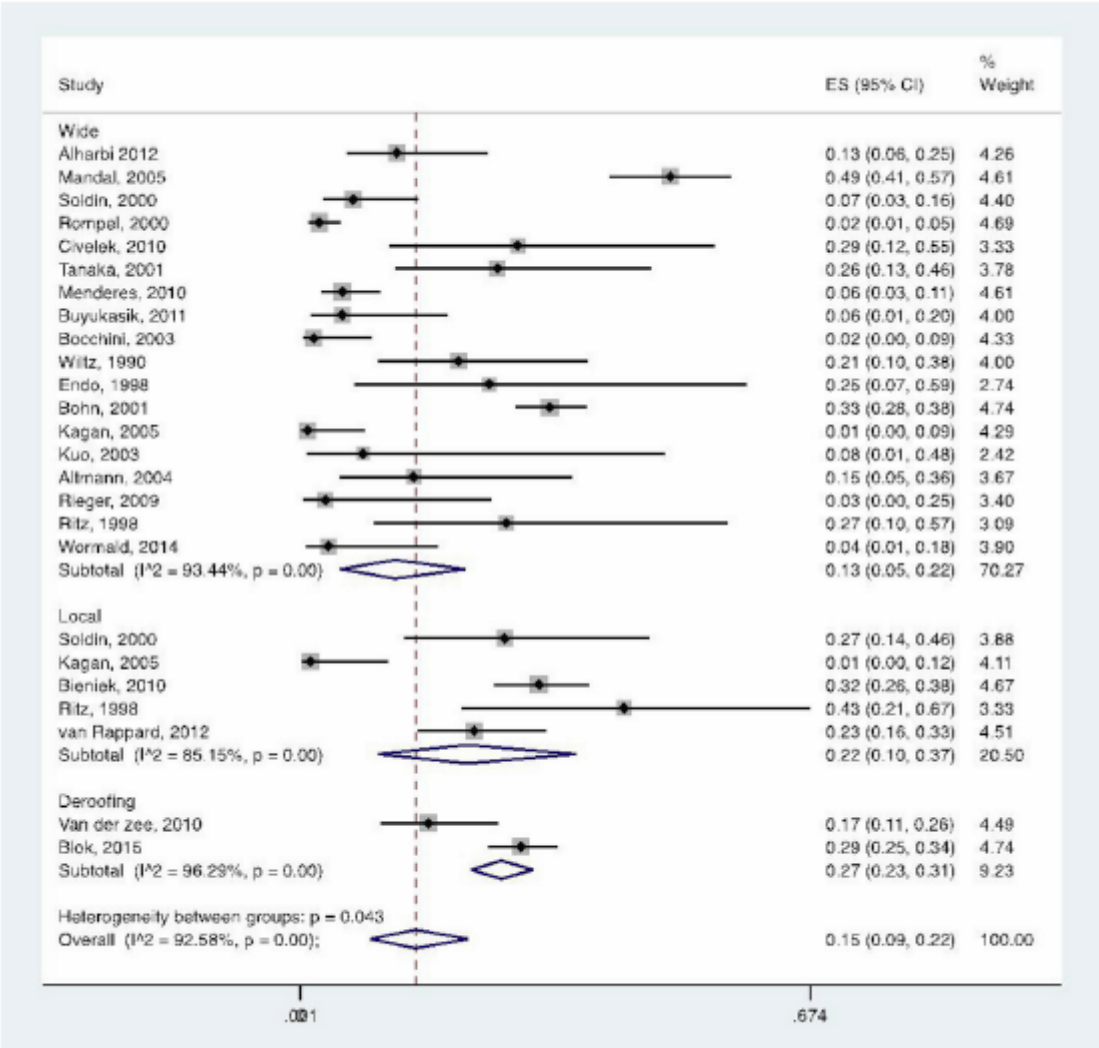


Fig 3. Hidradenitis suppurativa. Forest plot of recurrence rate by excision type.

Anmerkung/Fazit der Autoren

In conclusion, this review identified a high risk of HS recurrence post operatively. There was a higher rate of recurrence with minimally invasive surgeries. Surgical management is worth considering in localized disease, but high quality evidence is lacking for the role and timing of surgery combined with disease-controlling medical therapy. (…)

Kommentare zum Review

- Interstudy variable duration of follow-up, the different types of surgery, the severity or duration of HS before surgery, the area of surgery (ie, axilla, groin, perianal, etc.), and the lack of standardized methods for outcome assessment.
- Die Quelle erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, wird dieser SR jedoch ergänzend dargestellt.

3.4 Leitlinien

Ingram et al., 2018 [2].

British Association of Dermatologists

British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018.

Leitlinienorganisation/Fragestellung

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of hidradenitis suppurativa (HS).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- up to July 2018

LoE/GoR

- The strength of recommendation is expressed by the wording and symbols

Table 1 Strength of recommendation ratings

Strength	Wording	Symbols	Definition
Strong recommendation for the use of an intervention	'Offer' (or similar, e.g. 'Use', 'Provide', 'Take', 'Investigate', etc.)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy-makers, it would be a useful performance indicator
Weak recommendation for the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention, but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy-makers, it would be a poor performance indicator where variability in practice is expected
No recommendation		Θ	Insufficient evidence to support any recommendation
Strong recommendation against the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would not choose the intervention while only a small proportion would; for clinicians, most of their patients would not receive the intervention

Recommendations

- (GPP) Manage people with HS via a multidisciplinary team approach, particularly when considering surgical interventions.
- (GPP) In all people with HS, document the Hurley stage at baseline for the worst-affected region. For Hurley stage III (severe) disease consider immediate referral to dermatology secondary care.
- (GPP) Screen people with HS for associated comorbidities including depression, anxiety and cardiovascular risk factors (diabetes, hypertension, hyperlipidaemia and central obesity). If persistent gastrointestinal symptoms are reported refer for inflammatory bowel disease screening.
- (GPP) Where relevant, refer people with HS to smoking cessation services.
- (GPP) Where relevant, refer people with HS to weight management services.
- (GPP) Measure treatment response in people with HS using recognized instruments for pain and quality of life, including an inflammatory lesion count for those on adalimumab therapy.
- (GPP) In people with long-standing, moderate-to-severe HS, monitor for fistulating gastrointestinal disease, inflammatory arthritis, genital lymphoedema, cutaneous squamous cell carcinoma, and also for anaemia.
- (↑↑) Offer* oral tetracyclines such as doxycycline or lymecycline for at least 12 weeks to people with HS, considering treatment breaks to assess need for ongoing therapy and to limit the risk of antimicrobial resistance.
- (↑↑) Offer* combination treatment with oral clindamycin 300 mg twice daily and rifampicin 300 mg twice daily for 10–12 weeks to people with HS who are unresponsive to oral tetracyclines.
- (↑) Consider acitretin 0.3–0.5 mg $^{kg\text{-}1\ day\text{-}1}$ in males and nonfertile females with HS who are unresponsive to antibiotic therapies.
- (↑) Consider dapsone in people with HS who are unresponsive to antibiotic therapies.
- (↑↑) Offer* adalimumab (licensed for children and young people aged 12–17 years, and adults) 40 mg weekly to people with moderate-to-severe HS that is unresponsive to conventional systemic therapy.
- (↑) Consider infliximab 5 mg $^{kg\text{-}1}$ every 8 weeks in people with moderate-to-severe HS that is unresponsive to adalimumab therapy.
- (↑) Consider clindamycin 1% solution in people with HS.
- (↑) Consider intralesional corticosteroid injections for carefully selected, individual HS lesions during the acute phase.
- (GPP) Consider metformin in people with HS with concomitant diabetes mellitus, and females with HS and polycystic ovary syndrome or pregnancy.
- (↑) Consider extensive excision in people with HS to minimize recurrence rate.
- (↑) Consider extensive excision for people with HS when conventional systemic treatments have failed.
- (↑) Consider secondary intention healing [or TDAP (thoracodorsal artery perforator) flap closure for axillary wounds] in people with HS following extensive excision.

- (↓↓) Do not offer* isotretinoin to people with HS unless there are concomitant moderate-to-severe acneiform lesions of the face or trunk.
- (↓↓) Do not offer* adalimumab 40 mg every other week to people with moderate-to-severe HS that is unresponsive to conventional systemic therapy.
- (↓↓) Do not offer* etanercept to people with moderate to-severe HS that is unresponsive to conventional systemic therapy.
- (↓↓) Do not offer* cryotherapy to people with HS to treat lesions during the acute phase due to pain from the procedure.
- (↓↓) Do not offer* microwave ablation to people with HS.

Insufficient evidence to support any recommendation to:

- alitretinoin,
- anakinra,
- apremilast,
- atorvastatin,
- azathioprine,
- ciclosporin,
- colchicine,
- cyproterone,
- ethinyloestradiol with cyproterone acetate,
- ethinyloestradiol with norgestrel,
- finasteride,
- fumaric acid esters,
- hydrocortisone,
- hyperbaric oxygen therapy,
- intravenous antibiotics,
- isoniazid,
- laser and photodynamic therapies,
- MABp1 [anti-interleukin (anti-IL)-1 therapy],
- methotrexate,
- oral prednisolone,
- oral zinc,
- phototherapy,
- photochemotherapy,
- radiotherapy,
- secukinumab,
- spironolactone,
- staphage lysate,
- tolmetin sodium and
- ustekinumab for people with HS that is unresponsive to conventional systemic therapy.

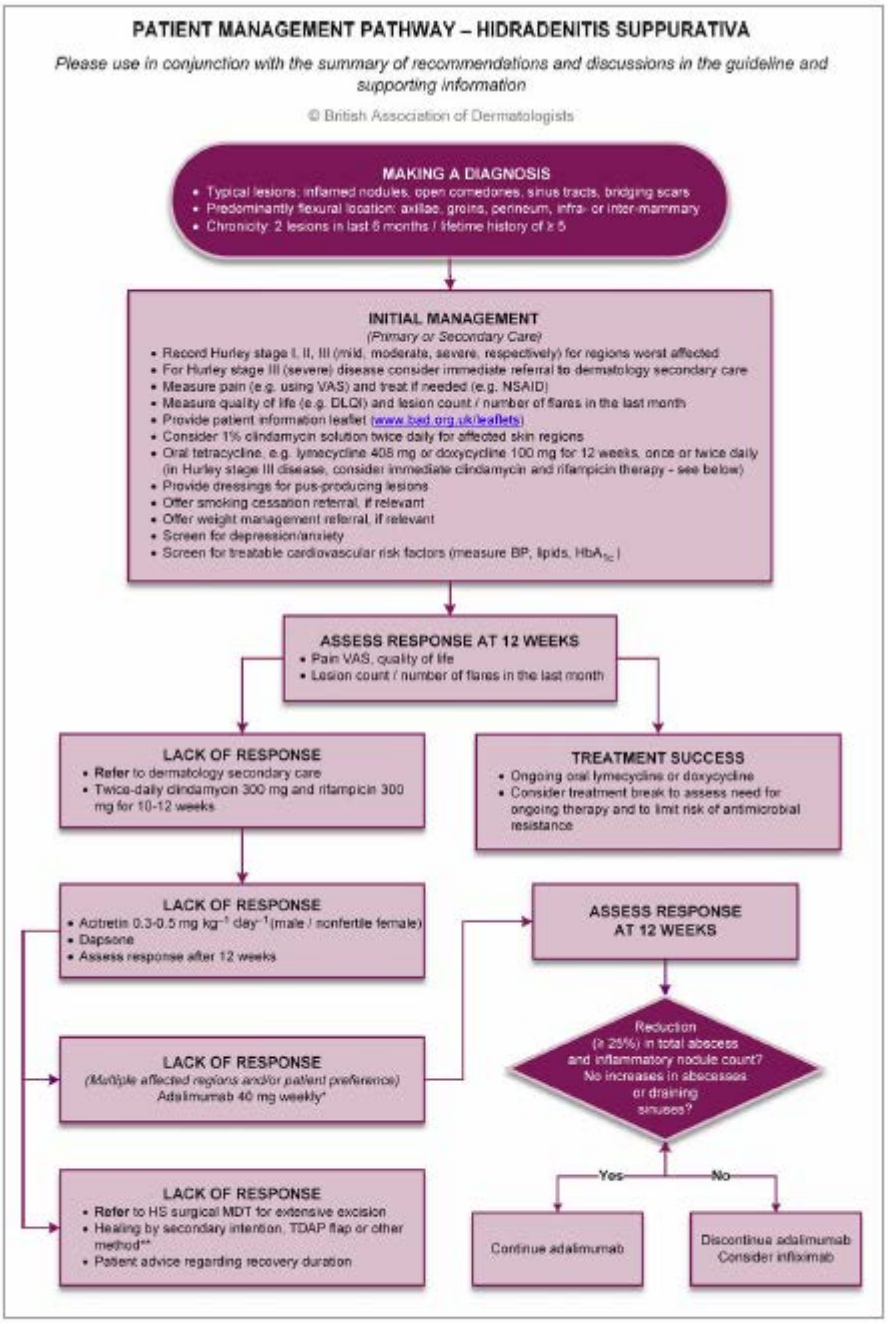


Fig 1. Management pathway for people with HS. *Licensed for use in those aged 12 years and above. **Surgical interventions are relatively underrepresented in the management pathway because evidence of high quality, in the form of randomized controlled trials, is sparse. BP, blood pressure; DLQI, Dermatology Life Quality Index; HS, hidradenitis suppurativa; MDT, multidisciplinary team; NSAID, nonsteroidal anti-inflammatory drug; TDAP, thoracodorsal artery perforator; VAS, visual analogue scale

Zouboulis et al., 2019 [7].

HS ALLIANCE working group

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

Leitlinienorganisation/Fragestellung

to develop international consensus recommendations for the treatment and management of patients with HS, which go beyond the current guidelines and provide practical suggestions on how tools and treatments should be used.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: Unklar ob Patienten repräsentiert;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed/Medline, The Cochrane Library, EMBASE, CINAHL, SCOPUS, BIOSIS and Web of Science between August 1996 and the date of this review (August 2016)

Recommendations

Table 1 Recommendations for assessment of comorbid disorders in patients with HS

What comorbidity-related screening should be assessed in patients with HS?	
Comorbidities and risk factors for HS include **(evidence level, grade of recommendation)**: • Smoking **(1, A)** • Cardiovascular disease **(2, B)** • Metabolic syndrome **(2, B)** • Obesity **(2, B)** • Depression **(3, B)** • Diabetes mellitus **(3, B)** • Hypertension **(3, B)** • Hypertriglyceridemia **(3, B)** • Spondyloarthropathy **(3, B)** • Crohn's disease **(4, C)** Treatment of HS should include careful assessment of comorbid disorders and risk factors, referral for appropriate diagnosis and treatment when needed and consideration of the impact of these factors on HS treatment decisions. Pretreatment screening should be performed where necessary	Consensus (93%) • 0% range 1–3 • 7% range 4–6 • 93% range 7–9
Weight loss/reduction in body mass index (obese patient; BMI ≥ 30) can be effective in reducing severity of disease in the long term[12,16] **(evidence level 4, grade of recommendation C).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
When assessing patients, particular emphasis should be paid to psychological comorbidity[18] **(evidence level 5, grade of recommendation D).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
In patients with chronic perianal and perineal HS, and in particular in the presence of fistulas, the possibility of Crohn's disease should be considered[21] **(evidence level 5, grade of recommendation D).**	Consensus (96%) • 4% range 1–3 • 0% range 4–6 • 96% range 7–9
The potential for malignant transformation in patients with chronic HS should be recognized[20] **(evidence level 5, grade of recommendation D).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9

Table 2 Recommendations for medical treatment of HS

Which non-biologic therapies are effective in the short, medium and long term for the treatment of HS?	
There are very few long-term data[26,33,34]	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
In Hurley stage II/III patients presenting with several active lesions, systemic clindamycin and rifampicin (dosage: 300 mg twice daily) should be administered for an average length of 10 weeks[24–27] **(evidence level 4, grade of recommendation C).** Local antibiotic guidelines should be followed The S1 European guidelines recommend that antibiotics should be used for up to 3 months and reintroduced in case of recurrence under the requirement that they were effective at the last time of use[1] **(evidence level 5, grade of recommendation D)**	Consensus (100%) [after revote] • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
Systemic acitretin may be considered as a third-line therapy for patients with mild/moderate HS[35–38] **(evidence level 4, grade of recommendation C).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
Which antibiotics are and are not efficacious for the treatment of HS and how should they be used?	
In Hurley stage I/II patients with mild localized HS with few lesions, topical clindamycin 1% is a possible therapy, especially in the absence of deep inflammatory lesions (abscesses).[23] The topical formulation may be administered twice daily for a maximum of 3 months. Resistance to clindamycin has changed since reviewed studies were completed; therefore, local antibiotic guidelines should be followed **(evidence level 2, grade of recommendation B).**	Consensus (92%) [after revote] • 0% range 1–3 • 8% range 4–6 • 92% range 7–9
In Hurley stage I/II patients presenting with several lesions and frequent exacerbations, the therapeutic group of systemic tetracyclines may be considered[23] **(evidence level 2, grade of recommendation B).** However, many countries use other derivatives from the same group (e.g. doxycycline, minocycline), for which there is no high-level evidence. Only one antibiotic of the same class should be used for a maximum of 12 weeks. Local antibiotic guidelines should be followed.	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
In Hurley stage II/III patients presenting with several active lesions, systemic clindamycin and rifampicin (dosage: 300 mg twice daily) should be administered for an average length of 10 weeks[24–27] **(evidence level 4, grade of recommendation C).** Local antibiotic guidelines should be followed.	Consensus (96%) • 0% range 1–3 • 4% range 4–6 • 96% range 7–9
A triple regimen of rifampicin (10 mg/kg once daily), moxifloxacin (400 mg once daily) and metronidazole (500 mg thrice daily) administered for up to 12 weeks, with metronidazole discontinuation at week 6, may offer efficacy in Hurley stage I and II patients, but should be used with appropriate monitoring[39] **(evidence level 4, grade of recommendation C).** Local antibiotic guidelines should be followed.	Consensus (81%) • 0% range 1–3 • 19% range 4–6 • 81% range 7–9
In selected patients with severe HS, a 6-week course of intravenous ertapenem (1 g daily) with consolidation treatment of rifampicin/moxifloxacin/metronidazole may be considered[40] **(evidence level 4, grade of recommendation C).** Local antibiotic guidelines should be followed.	Consensus (88%) • 0% range 1–3 • 12% range 4–6 • 88% range 7–9
Antibiotics studied in HS **(evidence level, grade of recommendation)**: • Topical clindamycin 1% **(2, B)** • Systemic tetracyclines **(2, B)** • Combination therapy of systemic clindamycin and rifampicin **(4, C)** • Triple regimen of rifampicin, moxifloxacin and metronidazole (single study) **(4, C)** • Intravenous ertapenem (single study) **(4, C)** • Systemic dapsone (single study)[41] **(4, C)**	Consensus (96%) • 0% range 1–3 • 4% range 4–6 • 96% range 7–9
There is no evidence for the use of other antibiotics	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
The S1 European guidelines recommend that antibiotics should be used for up to 3 months and reintroduced in case of recurrence under the requirement that they were effective at the last time of use[1] **(evidence level 5, grade of recommendation D).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
In HS, microbiological cultures are not useful **(evidence level 5, grade of recommendation D)**	Consensus (92%) • 0% range 1–3 • 8% range 4–6 • 92% range 7–9

How and when in the disease course of HS should biologics be introduced?	
There are few RCTs and little high-quality evidence	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
Adalimumab should be considered as first-choice biologic agent in moderate/severe HS after failure of conventional treatments[28–30] **(evidence level 2, grade of recommendation B).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
Infliximab has also been shown to be effective and should be considered as a second-line biologic for moderate/severe HS[31] **(evidence level 2, grade of recommendation B).**	Consensus (81%) • 4% range 1–3 • 15% range 4–6 • 81% range 7–9
Anakinra **(evidence level 2, grade of recommendation B)** has also been shown to be effective and should be considered as a third-line biologic for moderate/severe HS[32] Ustekinumab **(evidence level 4, grade of recommendation C)** is a potentially effective treatment for moderate/severe HS[42]	Consensus (84%) • 4% range 1–3 • 12% range 4–6 • 84% range 7–9
Etanercept is not effective for the treatment of HS[43] **(evidence level 2, grade of recommendation B).**	Consensus (96%) • 0% range 1–3 • 4% range 4–6 • 96% range 7–9
When should (any) combinations of medical treatments be considered for patients with HS and what combinations should be used?	
Evidence for the use of combination therapy in HS is limited	Consensus (92%) • 0% range 1–3 • 8% range 4–6 • 92% range 7–9
In Hurley stage II/III patients presenting with several active lesions, systemic clindamycin and rifampicin (dosage: 300 mg twice daily) should be administered for an average length of 10 weeks[24–27] **(evidence level 4, grade of recommendation C).** Local antibiotic prescribing guidelines should be followed.	Consensus (100%) [after revote] • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
A triple regimen of rifampicin (10 mg/kg once daily), moxifloxacin (400 mg once daily) and metronidazole (500 mg thrice daily) administered for up to 12 weeks, with metronidazole discontinuation at week 6, may offer efficacy in Hurley stage I and II patients, but should be used with appropriate monitoring[39] **(evidence level 4, grade of recommendation C).** Local antibiotic prescribing guidelines should be followed.	Consensus (100%) [after revote] • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
In Hurley stage I/II, the combination of oral zinc gluconate (30 mg thrice daily) and topical triclosan 2% (twice daily) may be considered as a treatment option[44] **(evidence level 4, grade of recommendation C).**	Consensus (81%) • 0% range 1–3 • 19% range 4–6 • 81% range 7–9
Intralesional steroids may be helpful for acute inflammatory nodules in combination with other treatments at all Hurley stages[45] **(evidence level 4, grade of recommendation C).**	Consensus (80.8%) • 11.5% range 1–3 • 7.7% range 4–6 • 80.8% range 7–9
Low-dose systemic corticosteroids (10 mg prednisolone equivalent per day) may be an effective adjunct in recalcitrant HS[46] **(evidence level 4, grade of recommendation C).** Long-term corticosteroid treatment should be used with appropriate caution.	Consensus (96%) • 0% range 1–3 • 4% range 4–6 • 96% range 7–9

Table 3 Recommendations for surgical treatment of HS

Which types of surgery may benefit patients with HS?	
Case and cohort studies used variable definitions of recurrence and a wide range of follow-up time and, therefore, cannot be compared.	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
In acute situations, surgical incision and drainage of tense and painful abscesses, i.e. fluctuant lesions, may be performed. However, incision and drainage should not be considered as a sole treatment because recurrence is almost inevitable[47–50] **(evidence level 4, grade of recommendation C).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
Surgical procedures, such as limited excision, deroofing and STEEP, can be used for solitary lesions of the disease. They could be performed for recurrent HS lesions at fixed locations or fistula/sinus tract formation in limited areas[51] **(evidence level 4, grade of recommendation C).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
Wide excision of the entire affected area, with removal of (non-)inflamed sinuses, nodules and scar tissue, may be performed in Hurley stage III to prevent recurrence[53–55] **(evidence level 4, grade of recommendation C).**	Consensus (96%) • 0% range 1–3 • 4% range 4–6 • 96% range 7–9
Chronic HS lesions that have not shown any signs of inflammation for a prolonged period of time may be excised to prevent further recurrence[56,57] **(evidence level 5, grade of recommendation D).**	Consensus (78%) • 7% range 1–3 • 15% range 4–6 • 78% range 7–9
Special attention should be paid to patients with perianal and/or perineal HS due to the possible existence of anal, urethral and vaginal fistulas and presence of squamous cell carcinoma[47,58] **(evidence level 4, grade of recommendation C).**	Consensus (92.6%) • 3.7% range 1–3 • 3.7% range 4–6 • 92.6% range 7–9
CO_2 ablative laser treatment is an effective alternative method to electrosurgical or cold steel techniques[59,60] **(evidence level 4, grade of recommendation C).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
How should medical and surgical treatments be integrated?	
There are no RCTs describing the combination of medical and surgical treatments	Consensus (92.6%) • 3.7% range 1–3 • 3.7% range 4–6 • 92.6% range 7–9
Pre- and postoperative biologic therapy may lead to a lower recurrence rate and a longer disease-free interval[61,62] **(evidence level 4, grade of recommendation C).**	Consensus (89%) • 0% range 1–3 • 11% range 4–6 • 89% range 7–9
There is no current literature regarding adverse events when integrating biologic therapy and surgery in HS patients. Studies in other immune-mediated diseases are insufficient to advise preoperative interruption of biologics **(evidence level 5, grade of recommendation D).**	Consensus (100%) • 0% range 1–3 • 0% range 4–6 • 100% range 7–9
Adalimumab reduces the need for surgical procedures (incisions and drainage)[29] **(evidence level 2, grade of recommendation C).**	Consensus (85.7%) • 3.6% range 1–3 • 10.7% range 4–6 • 85.7% range 7–9

Gulliver et al., 2016 [1].

Subcommittee of the European Dermatology Forum

Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa.

Leitlinienorganisation/Fragestellung

to produce a comprehensiveand rational approach for this debilitating and devastating chronic recurrent inflammatory disorder of the skin.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz: Angabe Suchzeitraum und Recherchestrategie fehlt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren teilweise dargelegt;
- Empfehlungen der Leitlinie sind größtenteils mit der zugrundeliegenden Evidenz verknüpft;
- Keine Angabe ob regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

Table 2 Category or Evidence/ Strength of Recommendation Rating Scale

Category of Evidence	Strength of Recommendation
Ia: Meta-analysis of randomized controlled trials	A: Category I evidence
Ib: Randomized controlled trial	
IIa: Controlled study without randomization	B: Category II evidence or extrapolated from category I evidence
IIb: Quasi-experimental study	
III: Non-experimental descriptive studies such as comparative, correlation and case-control studies	C: Category III evidence or extrapolated from category I or II evidence
IV: Expert committee reports or opinion or clinical experience of respected authorities, or both	D: Category IV evidence or extrapolated from category II or III evidence

Guyatt G, Oxman AD, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ April 2008; 336: 924. Last accessed February 2014.

Sonstige methodische Hinweise

- Die LL erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, wird sie jedoch ergänzend dargestellt.

Recommendations

Therapy	Category of Evidence	Strength of Recommendation
1st Line		
Clindamycin (topical) [1]	IIb	Possible B
Clindamycin/Rifampicin (oral) [2]	III	C
Adalimumab (subcutaneous) [3]	Ib	A
Tetracycline (oral)	IIb	B
Surgery		
Excision or Curettage of Individual Lesions	III	C
Total Excision of the Lesions and Surrounding Hair-Bearing Skin	IIb	B
Second Intention Healing	IIb	B
Primary Closure	III	C
Reconstruction with Skin Grafting & NPWT	III	C
Reconstruction with Flap Plasty	Ia/IIa	A/B
Deroofing	IV	D
Carbon Dioxide Laser Therapy	Ib	A
Nd:YAG Laser	Ib	A
IPL	IV	D
2nd Line		
Zinc Gluconate	III	C
Resorcinol	III	C
Intralesional Corticosteroids	IV	D
Systemic Corticosteroids	IV	D
Infliximab	Ib/IIa	B
Acitretin/Etretinate	III	C
3rd Line		
Colchicine	IV	D
Botulinum Toxin	IV	D
Isotretinoin	IV	D
Dapsone	IV	D
Cyclosporine	IV	D
Hormones	IV	D
Pain Control		
NSAIDS	IV	D
Opiates	IV	D
Dressings		
No studies have been published to date on the use of specific dressing or wound care methodology in HS. Choice of dressing is based on clinical experience.	IV	D

1. Single double-blind, placebo-controlled, randomized trial. Hurley stage 1–2.
2. Evaluated in case series.
3. Multiple prospective randomized, double-blind, placebo-controlled trials (Pioneer 1 and 2).

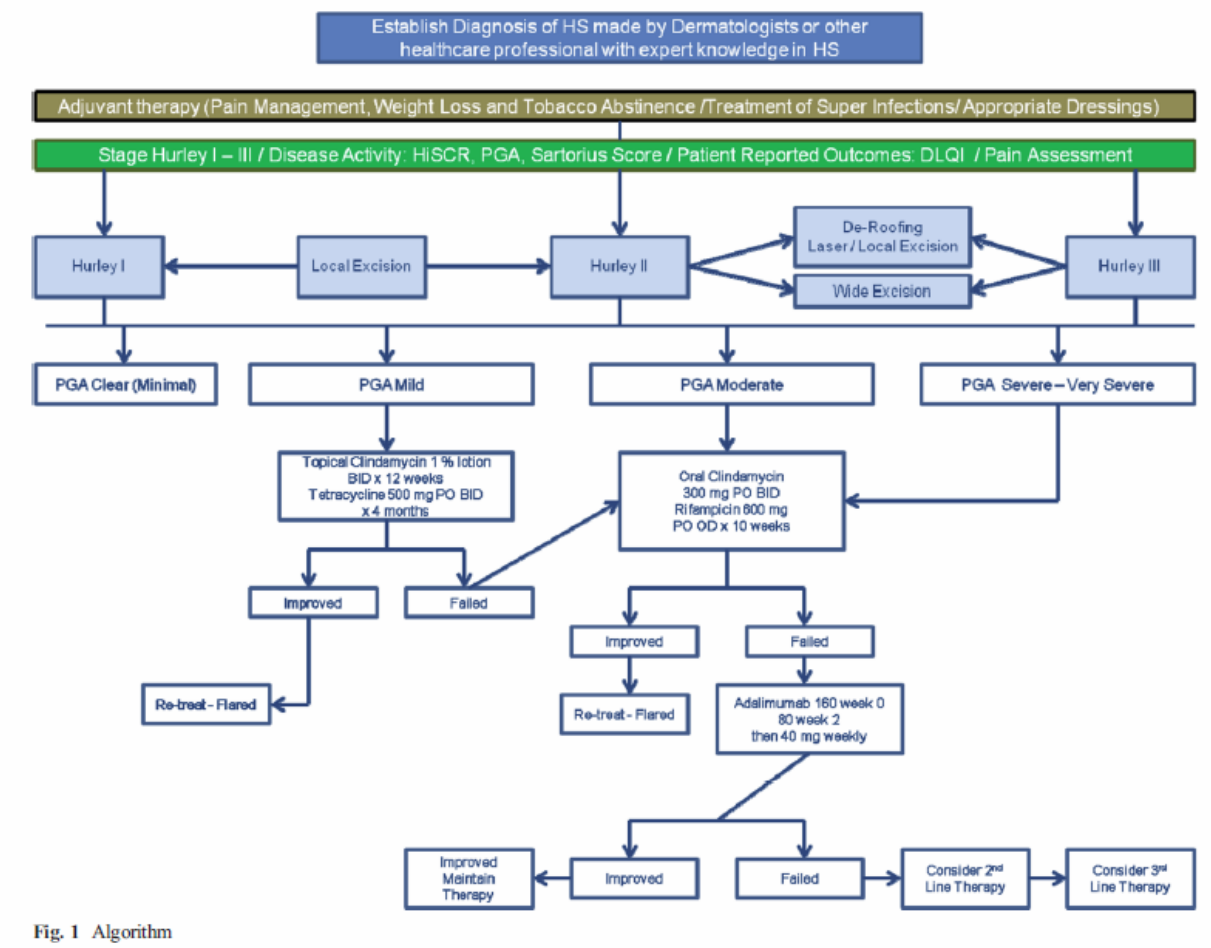


Fig. 1 Algorithm

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2019) am 03.04.2019

#	Suchfrage
1	[mh "hidradenitis suppurativa"] explode all trees
2	(acne and invers*):ti,ab,kw
3	(hidradeniti* and suppurativ*):ti,ab,kw
4	(velpeau* or verneuil*):ti,ab,kw and disease*:ti,ab,kw
5	(pyodermia fistulans sinifica):ti,ab,kw
6	#1 or #2 or #3 or #4 or #5
7	#6 Publication Year from 04.2014 to 04.2019
8	#7 Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 03.04.2019

#	Suchfrage
1	hidradenitis suppurativa[mh]
2	acne[tiab] AND invers*[tiab]
3	hidradeniti*[tiab] AND suppurativ*[tiab]
4	(velpeau*[tiab] OR verneuil*[tiab]) AND disease*[tiab]
5	pyodermia fistulans sinifica[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR

	treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	((#7) AND ("2014/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 03.04.2019

#	**Suchfrage**
1	hidradenitis suppurativa[mh]
2	acne[tiab] AND invers*[tiab]
3	hidradeniti*[tiab] AND suppurativ*[tiab]
4	(velpeau*[tiab] OR verneuil*[tiab]) AND disease*[tiab]
5	pyodermia fistulans sinifica[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(((#7) AND ("2014/04/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
9	(#8) NOT retracted publication[ptyp]

Referenzen

1. **Gulliver W, Zouboulis CC, Prens E, Jemec GB, Tzellos T.** Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the european guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord 2016;17(3):343-351.
2. **Ingram JR, Collier F, Brown D, Burton T, Burton J, Chin MF, et al.** British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. Br J Dermatol 2018.
3. **Ingram JR, Woo PN, Chua SL, Ormerod AD, Desai N, Kai AC, et al.** Interventions for hidradenitis suppurativa. Cochrane Database of Systematic Reviews [online]. 2015(10):CD010081. URL: http://dx.doi.org/10.1002/14651858.CD010081.pub2.
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7. **Zouboulis CC, Bechara FG, Dickinson-Blok JL, Gulliver W, Horvath B, Hughes R, et al.** Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. J Eur Acad Dermatol Venereol 2019;33(1):19-31.