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Hidradenitis Suppurativa
Advances in Diagnosis and Treatment

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IMPORTANCE Hidradenitis suppurativa (HS) is relatively common, with the prevalence of 0.05% to 4.10%, yet many patients receive inadequate treatment.

OBJECTIVE To review the diagnosis, epidemiology, and treatment of HS with an emphasis on advances in the last 5 years.

EVIDENCE REVIEW A literature search was conducted using PubMed, MEDLINE (Medical Subject Headings [MeSH]), and EMBASE to include recently published treatment studies (searched from September 1, 2011, to May 1, 2017). Reviews, guidelines, conference abstracts, and studies with less than 10 patients were excluded. Furthermore, internet searches for guidelines on hidradenitis suppurativa using Baidu, Bing, Google, and Qwant browsers were performed.

FINDINGS The diagnosis of HS is made by lesion morphology (nodules, abscesses, tunnels, and scars), location (axillae, inframammary folds, groin, perigenital, or perineal), and lesion progression (2 recurrences within 6 months or chronic or persistent lesions for ≥3 months). HS is more common than was previously thought based on epidemiological analysis (0.05%-4.10%). Disability from HS can be significant. Patients with HS may have significant comorbidities (eg, obesity, metabolic syndrome, diabetes, and arthritis) and increased all-cause mortality (incidence rate ratio, 1.35 [95% CI, 1.15-1.59]). Antibiotic treatment with combinations of clindamycin and rifampicin, or ertapenem followed by combination rifampicin, moxifloxacin, and metronidazole for 6 months is effective. Adalimumab is effective in a significant proportion of patients and treatment with IL-1 and IL-12 receptor subunit beta 1 (Rb1) antibodies may also be useful. Tissue-sparing surgical techniques and carbon dioxide laser treatments also are available, but the evidence on clinical outcomes with these approaches is limited.

CONCLUSIONS AND RELEVANCE Hidradenitis suppurativa is more common than previously thought and may be treated by an array of pharmacological and surgical techniques. Hidradenitis suppurativa should be considered in the differential diagnosis of nodular lesions or sinus tracts present in the axillae, groin, perineal, and mammillary fold regions.

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Supplemental content

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Hidradenitis suppurativa (HS) is an inflammatory skin disease with a characteristic clinical presentation of recurrent or chronic painful or suppurating lesions in the apocrine gland–bearing regions (**Figure 1** and **Figure 2**).[1,2] HS should be differentiated from infections such as furuncles, carbuncles, and abscesses (due to infectious agents and response to antibiotics), cutaneous Crohn disease (often concurrent with gastrointestinal Crohn, has "knife-cut" ulcers, and no comedones [whiteheads or blackheads]), and acne (distributed on the face and upper truncus, whereas HS predominantly affects intertriginous areas) (**Table 1**).

Surveys show that the mean delay in establishing a diagnosis of HS from the time of its initial presentation is 7.2 years.[3] This may be because of insufficient awareness of HS or that patients may accept recurrent symptoms that follow standard treatments and not seek further care.

Etiology, Pathogenesis, and Epidemiology

HS is a disease of hair follicles characterized by a perifollicular lymphocytic infiltrate with subsequent sebaceous gland loss (**Figure 3**).[4] This process may result from deregulation of the local immune system.[5] As HS progresses, increased levels of interleukin (IL)-1, tumor necrosis factor (TNF), IL-17, S100A8, S100A9, caspase-1, and IL-10 appear in the tissue accompanied by an influx of neutrophils, monocytes, and mast cells.[5-7]

Early lesions have normal bacterial flora for the skin region, suggesting that bacterial infection is secondary to the underlying inflammatory process and that the inflammation is not caused by

an infection.[8] As inflammation progresses, tissue destruction releases follicular content into the surrounding tissues causing the inflammatory process to spread. As healing from the inflammatory process occurs, tunneling and tissue scarring occur (Figure 1).

The estimated prevalence of HS varies from 0.05% to 4.10%, depending on the methodology used to estimate the prevalence.[9,10] The lower estimates are derived from registry studies and the higher ones from prospective or self-reported studies.

Disease severity is traditionally classified according to the Hurley classification,[11] which defines stage I as transient nonscarring inflammatory lesions; stage II as separate lesions consisting of recurrent abscesses with tunnel formation and scarring, and single or multiple lesions separated by normal-looking skin; and stage III as coalescent lesions with tunnel formation, scarring, and inflammation (Figure 1). Hurley classification is, however, not suited for dynamic assessment of HS and a large number of scores have been devised but not validated. The modified Sartorius Score (mSS) in which involved anatomical predetermined regions are counted and, in addition, inflammatory and noninflammatory lesions are counted, classified, and weighted according to type. Additional points are given for the longest distance between 2 lesions within each affected anatomical region and for any regions containing Hurley stage III. The points are added for an overall severity score.[12] The HS-Physician's Global Assessment (HS-PGA; an objective total count of HS lesions) is also used. It is an anchored 6-point PGA based on lesion counts in predilection areas.[13] Currently, an international effort is under way to identify and validate core outcomes for HS.[14]

HS *hidradenitis suppurativa*

HiSCR-50 *hidradenitis suppurativa clinical response, defined as ≥50% improvement in inflammatory lesions count*

mSS *modified Sartorius score*

STEEP *skin tissue–sparing excision with electrosurgical peeling*

Morbidity

HS lesions are very pruritic, painful, and located in the intertriginous areas and can be malodorous and have a purulent discharge. This constellation of problems results in substantial disability and social stigma. Because HS lesions tend to locate in the groin area, HS can adversely influence a patient's sexual health.[15,16] Depression and anxiety may occur in these patients.[10,17-20] A number of associated physical comorbidities also occur (eg, obesity, metabolic syndrome, diabetes, arthritis, Crohn disease, and polycystic ovary disease).[21]

Methods

A literature search was conducted using PubMed, MEDLINE (Medical Subject Headings [MeSH]), and EMBASE from September 1, 2011, to May 1, 2017. Reviews, guidelines, conference abstracts, and articles reporting the results from less than 10 patients were excluded. Grading of Recommendations Assessment, Development, and Evaluation (GRADE; levels of evidence: A, high level; B, moderate; C, low; D, very low) was used to assess the overall quality of the evidence. An internet search for guidelines was conducted and further details about the PRISMA flow diagrams and literature search are presented in Supplement 1 and in the eAppendix in Supplement 2, respectively.

Key Points

Question How has the diagnosis and treatment of hidradenitis suppurativa (HS) recently changed?

Findings Weight reduction is important for obese patients. Drug treatment usually begins with systemic antibiotics although this approach is based on clinical experience rather than through randomized clinical trials. Adalimumab is the first drug specifically approved by the US Food and Drug Administration for the treatment of HS, but other biologics are useful. Newer surgical approaches include skin tissue–sparing excision with electrosurgical peeling (STEEP) and carbon dioxide laser evaporation.

Meaning Hidradenitis suppurativa has a new array of medical and surgical treatments to facilitate its treatment.

Recent Advances in Treatment

Topical Agents

There have been no recent studies of topical agents (**Table 2**). Older studies have shown that resorcinol (15%) may be helpful.[32-34] Topical disinfectants, such as chlorhexidine, peroxides, and permanganate soaks, are frequently used, but there is little evidence to suggest that they are effective.

Intralesional Treatment

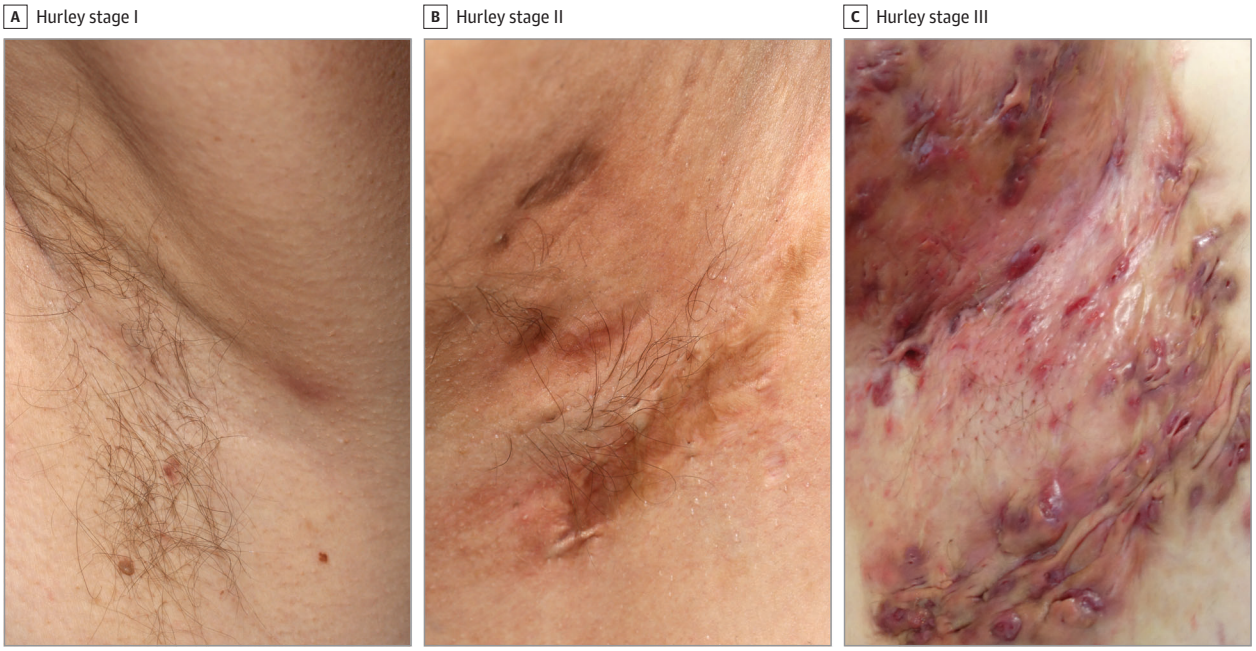
Injection of triamcinolone acetonide into HS lesions has been used, but evidence for this approach is limited. In a prospective case series of 36 patients, triamcinolone (10 mg/mL) was injected into HS lesions. Pain was significantly reduced on the day following the injection (from a score of 5.5 to 2.3 on a 0-10 point numerical rating scale [0 indicating no pain and 10 indicating the worst pain imaginable], $P < .005$). After 1 week of injection therapy, there was a reduction in erythema (median score from 2-1 on a 5-point anchored rating scale [0-4: 0 indicating normal-appearing skin in all aspects and 4 indicating dark red erythema], $P < .001$), edema (median score from 2-1, $P < .001$), suppuration (median score from 2-1, $P < .001$), and lesion size (median score from 3-1, $P < .001$).[22] The long-term efficacy of this approach remains to be established.

Antibiotics

Antibiotics are commonly used to treat HS flares because of secondary bacterial infections and some, such as tetracycline, ampicillin, ciprofloxacin, and rifampicin, also help manage HS because they might also have immunomodulatory properties. For example, tetracycline suppresses neutrophil migration, chemotaxis, and inhibits matrix metalloproteinase.[35,36]

Because HS is a chronic disease that is difficult to distinguish from a primary infective process, there is a tendency to treat it with antibiotics that might cause antimicrobial resistance. Clindamycin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant and methicillin-resistant *S aureus*, or combination trimethoprim and sulfamethoxazole–resistant *Proteus* species bacteria were more common in patients with HS who were treated with topical clindamycin, oral ciprofloxacin, or oral combination trimethoprim and

Figure 1. Typical Hidradenitis Suppuration (Hurley Stage I, II, and III)



The 3 different Hurley stages in the axillae region. Hurley stage I (inflamed lesion without scarring); Hurley stage II (tunnels, scars, and inflamed nodules separated by clinically unaffected skin); and Hurley Stage III (coalescent lesions [inflamed tunnels, nodules, scars]).

sulfamethoxazole compared with those not using antibiotics. No significant antimicrobial resistance was observed when tetracyclines or oral clindamycin was used.[37]

Topical Antibiotics

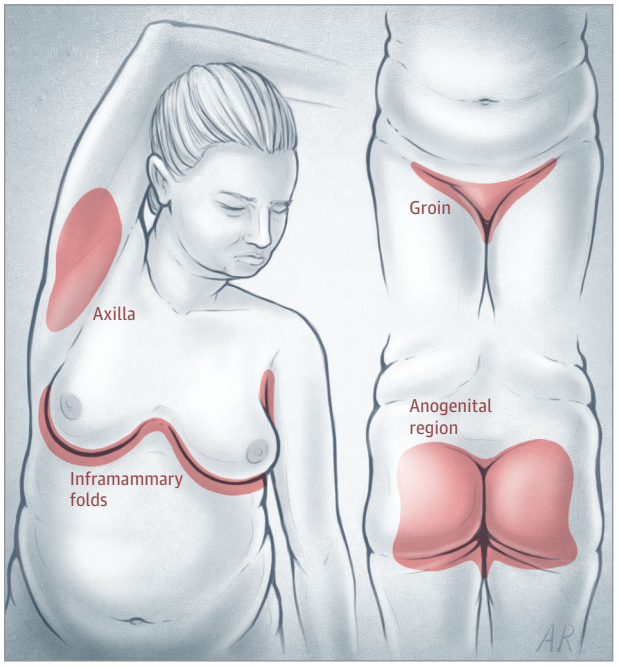
Topical clindamycin (0.1% twice daily) has been studied in clinical trials, and randomized clinical trials (RCTs) found topical clindamycin to be more effective than placebo.[38] Oral tetracycline (500 mg twice daily) has equivalent outcomes to topical clindamycin for Hurley stage I and II when the outcomes are measured by counting the number of nodules and abscesses and assessing a patient's soreness along with physician evaluation of the lesions.[39]

Systemic Antibiotics

Although systemic antibiotics have been used to treat HS, high-quality evidence to support this practice is lacking. It is not uncommon for clinicians to administer combination therapy of clindamycin (300 mg twice daily) and rifampicin (300 mg twice daily) for 10 weeks. This regimen was initially described in 2006 in a small retrospective study that included 14 patients and the outcomes of this regimen have been described in several other small studies.[40] Because of the limitations of these studies, little is known about long-term follow-up and recurrence of HS after this treatment regimen is given.[25]

A prospective study in which oral clindamycin and rifampicin were given to patients for 12 weeks with 1-year follow-up reported an initial clinical response (response defined as ≥50% improvement in inflammatory lesions count [HiSCR-50]) in 19 of 26 patients (73%) immediately following the treatment then decreasing to 7 of 17 patients (41%) at 1 year. The remaining 10 of 17 patients (59%) relapsed a mean of 4.2 months (SD, 3.99; relapse range, 1-12 months) after treatment.[24] Adverse events occurred in 1 of 3 patients; diarrhea and nausea being the most common. These data suggest that clindamycin and rifampin regimens have limited efficacy.

Figure 2. Typical Hidradenitis Suppuration Distribution

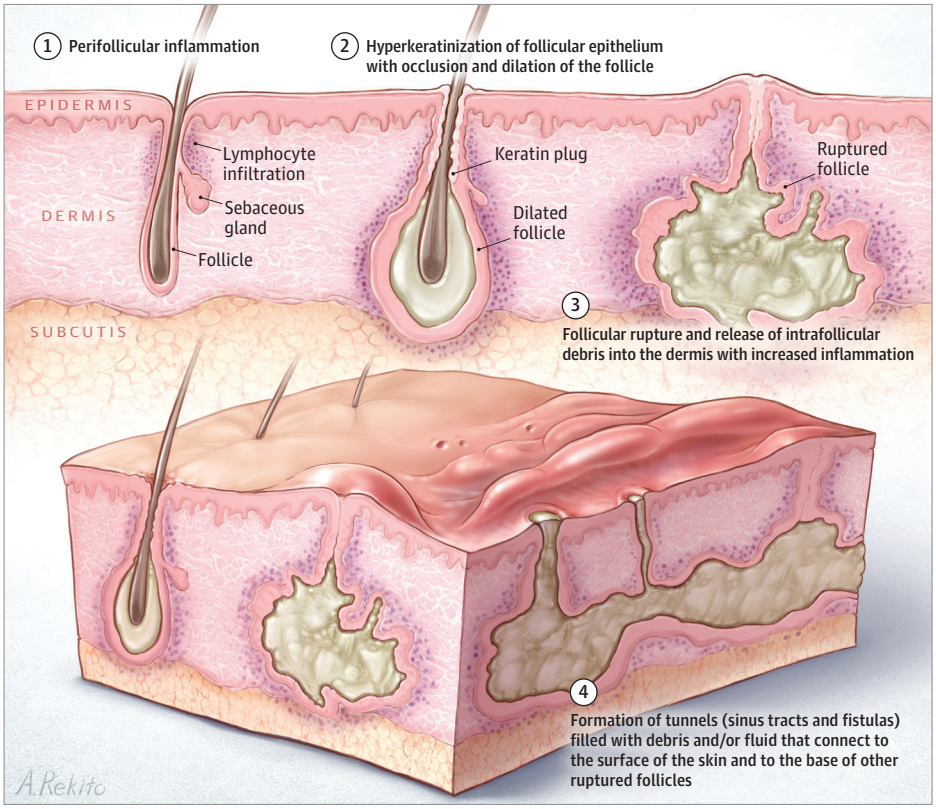


Hidradenitis suppurativa is located in the intertriginous areas.

Table 1. Differential Diagnosis of Hidradenitis Suppurativa

Differential Diagnosis	Common Features With Hidradenitis Suppuration	Differentiation
Cutaneous morbus Crohn disease	Perianal and genital fistulas, abscesses, scars	"Knife-cut" ulcers; fistulas communicate with the gastrointestinal tract; often concurrent with gastrointestinal Crohn disease; no comedones (blackheads)
Acne	Cysts with pus, inflammatory nodules, scars	Distribution on the face, back, and upper chest, comedones (whiteheads)
Intergluteal pilonidal disease	Sinus tract formation; swollen, inflamed, and painful lesions; can occur in patients with hidradenitis suppurativa	Localization and recurrence is limited to the intergluteal area
Follicular pyoderma, furuncles, carbuncles, and abscesses	Nodules and abscesses; purulent drainage; can occur in intertriginous areas	Mainly due to an infectious agent; burning and perilesional erythema; fluctuating lesion; drains on incision; transient condition; has random distribution; responds rapidly to antibiotics
Granuloma inguinale (donovanosis)	Localization in the genital and inguinal folds	Red ulcers; granulation of tissue; bleeds easily; has Donovan bodies (histology); infectious agent: *Klebsiella granulomatis*
Lymphogranuloma venereum	Localization in the genital and inguinal folds	Bacterial etiology: *Chlamydia trachomatis* (serotype L1-L3)
Actinomycosis	Fistulas or sinus tracts	Bacterial infection caused by *Actinomyces*
Cat scratch disease	Papulopustular lesions; granulomatous and suppurative, subacute regional lymphadenitis	History of a scratch or bite from a cat, *Bartonella* infection
Cutaneous tuberculosis	Purulent drainage; abscesses; fistulas	Bacterial infection caused by *Mycobacterium*
Steatocystoma multiplex	Draining inflamed nodules	Follicular tumors also on convex skin surfaces
Metastasis	Inflamed nodules	Asymmetrical; often painless

Figure 3. Pathogenesis of the Hidradenitis Suppurativa Lesion



One study of 20 patients[23] treated with 100 mg of minocycline daily combined with 0.5 mg of colchicine twice daily for 6 months and then a maintenance regimen of 0.5 mg of colchicine twice daily for 3 months found that 40% of the patients experienced excellent results (HS-PGA score range, 75%-100%), 55% of the patients experienced good results (HS-PGA score range, 50%-75%), and 5% of the patients experienced fair results (HS-PGA score range, 25%-50%) at 9 months. Three patients experienced nausea and diarrhea, but they were able to continue the therapy.[23]

A prospective study of 30 patients receiving 6 weeks of ertapenem (1 g daily) with subsequent rifampicin (10 mg/kg once daily), moxifloxacin (400 mg once daily), and metronidazole (500 mg; 3 times daily) combination treatment for 6 weeks, further followed

Table 2. Medical Treatment Studies About Hidradenitis Suppurativa Published in the Last 5 Years

Study	Drug	Study Type (Evidence Level)	Hurley Stage (% of Patients)	Regimen	Follow-Up	Outcome (% of Patients)	Most Common Adverse Effects (% of Patients)
Topical Treatment							
Riis et al[22] (N = 36)	Triamcinolone	Case-series (low)	NA	NA	1 wk	At day 1, pain reduction; at day 7, inflammation reduction	NR
Systemic Antibiotic Treatment							
Armyra et al[23] (N = 20)	Tetracycline and colchicine	Prospective, pilot study (low)	I (5), II (75), and III (20)	0-6 mo: minocycline (100 mg daily) and colchicine (0.5 mg twice daily); maintenance dose 6-9 mo: colchicine (0.5 mg twice daily)	9 mo	Significant clinical improvement (Hurley stage/DLQI)	Nausea and diarrhea
Dessinioti et al[24] (N = 26)	Clindamycin and rifampicin	Prospective hospital-based study (low)	I (15), II (62), and III (23)	Clindamycin (600 mg daily) and rifampicin (600 mg daily) for 12 wk	12 wk and 1 y	HS-PGA score improvement and ≥50% reduction in inflammatory lesions from baseline at 12 weeks (73) and at 1 y (41)	Diarrhea, nausea, hypercholesterolemia, vaginitis, or causalgia (31)
Bettoli et al[25] (N = 23)	Clindamycin and rifampicin	Prospective noncomparative study (low)	NA	Clindamycin (600 mg daily) and rifampicin (600 mg daily) for 10 wk	10 wk	mSS score improvement ≥25% (85); 17 of 20 patients	Nausea and vomiting (13)
Join-lambert et al[26] (N = 30)	Ertapenem, rifampicin, moxifloxacin, and metronidazole	Prospective noncomparative study (low)	I (in 43 anatomical regions), II (in 50 anatomical regions), and III (in 40 anatomical regions)	Initial treatment: ertapenem (1 g daily) for 6 wk Consolidation treatment: rifampicin (10 mg/kg daily) and moxifloxacin (400 mg daily) and metronidazole (500 mg 3 times daily) for 6 wk; followed by rifampicin (10 mg/kg once daily) and moxifloxacin (400 mg once daily) 6 wk **After consolidation treatment:** Clinical remission treatment: co-trimoxazole (400 mg daily) Resistant or relapsing treatment: <5-cm lesions: rifampicin (10 mg/kg daily) and moxifloxacin (400 mg daily) and metronidazole (500 mg 3 times daily) for 6 weeks >5-cm lesions: ceftriaxone (1 g daily) and metronidazole (500 mg 3 times daily) for 3 weeks followed by rifampicin (10 mg/kg daily) and moxifloxacin (400 mg daily) and metronidazole (500 mg 3 times daily) for 3 wk	24 wk	Change in mSS Initial treatment: mean mSS score at baseline, 49.5 (range, 28-62); mean mSS score after ertapenem: 19.0 (range, 12-28) Consolidation treatment: clinical remission (59)	Initial treatment: oral and vaginal candidiasis (27), gastrointestinal symptoms (20), headache (13), asthenia (17) Consolidation treatment: gastrointestinal symptoms (60), oral and vaginal candidiasis (50)
Biologics Treatment							
Kimball et al[27] (N = 307)	Adalimumab	PIONEER I, phase 3, double-blind, RCT (high)	II (≈ 52) and III (≈ 47-48)	Period 1: adalimumab (40 mg/wk) or matching placebo for 12 wk Period 2: adalimumab (40 mg/wk or 40 mg EOW) or placebo for 24 wk	36 wk	HiSCR-50 Period 1: adalimumab every wk (41.8), placebo, (26.0), P = .003 Period 2: adalimumab every wk (37-52.4); adalimumab EOW (17.9-50.0); placebo (25.9-27.3)	Any (most common: infections, headache, nasopharyngitis) Period 1: placebo (58.9); adalimumab every wk (50.3) Period 2: placebo (57.1); adalimumab every wk (58.3-62.1); adalimumab EOW (45.8)
Kimball et al[27] (N = 326)	Adalimumab	PIONEER II, phase 3, double-blind, RCT (high)	II (≈ 53-55) and III (≈ 45-47)	Period 1: adalimumab (40 mg/wk) or matching placebo 12 weeks Period 2: adalimumab (40 mg/wk or 40 mg EOW) or placebo for 24 wk	36 wk	HiSCR-50 Period 1: adalimumab every wk (58.9); placebo (27.6) Weekly vs placebo (0.001) Period 2: adalimumab every wk (40.0-43.8); adalimumab EOW (9.5-45.2); placebo (15.9-35.5)	Any (most common: infections, headache, nasopharyngitis) Period 1: placebo (63.2); adalimumab every wk (57.1) Period 2: placebo (45.0-64.7); adalimumab every wk (56.9); adalimumab EOW (56.6)

(continued)

Table 2. Medical Treatment Studies About Hidradenitis Suppurativa Published in the Last 5 Years (continued)

Study	Drug	Study Type (Evidence Level)	Hurley Stage (% of Patients)	Regimen	Follow-Up	Outcome (% of Patients)	Most Common Adverse Effects (% of Patients)
Kimball et al[28] (period 1: n =154; period 2: n=142)	Adalimumab	Phase 2, parallel, RCT Period 1: blinded Period 2: open-label (high)	I and II (≈ 70%) and III (≈ 30%)	Period 1: adalimumab (40 mg/wk or 40 mg EOW) or matching placebo for 16 wk Period 2: adalimumab (40 mg every other wk) for 36 wk (switched to weekly dosing if HS-PGA score was moderate or worse at wk 28 or 31)	Period 1: 16 wk Period 2: 52 wk	HS-PGA score of clear, minimal, or mild with at least 2 GRADE levels of improvement Period 1: placebo (3.9); adalimumab EOW (9.6); adalimumab every wk (17.6) Period 2: adalimumab (15); dose-escalated at wk 28 or 31 (63)	Most common: headache, upper respiratory tract infection, hidradenitis, nausea, nasopharyngitis (>10 overall) Serious adverse event: placebo (3.9); adalimumab EOW (5.8); adalimumab every wk (7.8)
Sotiriou et al[29] (N = 15)	Adalimumab	Prospective, open-label clinical trial (moderate)	II and III (NA)	Adalimumab (80 mg) at baseline followed by (40 mg/wk) for 6 mo	24 wk and 48 wk	Change in mSS and DLQI Baseline to wk 24: mSS decreased from 38.6 to 16.5 (P = .001); DLQI decreased from 15.9 to 4.8 (P = .001) Follow-up at wk 48: mSS increased to 32.4 (significant reduction from baseline to final mSS score [P = .002]); DLQI increased to 12.2 (significant reduction from baseline to final DLQI score [P = .005])	Change in VAS score Baseline to wk 24: VAS score decreased 8.9 to 0.7 (P = .001) Follow-up at wk 48:VAS score increased to 7 (significant reduction from baseline to final VAS score [P = .008])
Blok et al[30] (N = 17)	Ustekinumab	Prospective, uncontrolled, open-label design (low)	II and III (NA)	Ustekinumab (45 mg or 90 mg) at wk 0, 4, 16, and 28	40 wk	HiSCR-50 (47) and moderate to marked improvement in mSS (82)	Most common: headache, fatigue and upper respiratory tract infections
Tzanetakou et al[31] (N = 20)	Anakinra	RCT (moderate)	II (53) and III (47)	Subcutaneous anakinra (100 mg daily) for 12 wk	24 wk	Decrease in disease activity score Placebo (30); treated (78) (P = .04)	Diarrhea (11), swelling at the injection site (11), vaginal candidiasis (11)

Abbreviations: DLQI, Dermatology Quality of Life Index; EOW, every other week; HiSCR-50, hidradenitis suppurativa clinical response 50%; mSS, modified Sartorius score; NA, not available; NR, none reported; HS-PGA, Hidradenitis Suppurativa-Physician's Global Assessment; RCT, randomized clinical trial; VAS, visual analog scale.

by rifampicin (10 mg/kg once daily) and moxifloxacin alone (400 mg once daily) for 6 weeks suggested this approach was effective (a decrease in mSS and clinical remission of 59% of HS areas at 6 months of follow-up).[26] However, this study was small and required long-term intravenous administration of an expensive antibiotic and is probably not a practical solution for HS.

Anti-inflammatory Treatment

Because new monoclonal antibody therapies have been studied with the intent of gaining regulatory approval, there is higher-quality evidence for these treatments than for antibiotics.

Adalimumab

Adalimumab is a recombinant human IgG1 anti-TNF monoclonal antibody that binds and blocks the proinflammatory cytokine TNF-α.[41] Adalimumab was assessed in an open-label trial of 15 patients treated with 80 mg of adalimumab at baseline followed by 40 mg weekly for 24 weeks. The mSS declined from 38.6 at baseline to 16.5 at week 24 (P = .001; z = −3.411; 95% CIs were not available) but increased to 32.4 (P = .001; z = −3.297; 95% CIs were not available) at follow-up week 48.[29]

A phase 2 RCT of adalimumab in HS compared 152 patients randomized into 3 groups. One group received injections of 40 mg of adalimumab every week (EW group) from week 4 (initial dose of 160 mg at baseline, 80 mg at week 2), another group received 40 mg of adalimumab every other week (EOW group; week 1 through week 15 after initial dose of 80 mg at baseline), and the third group received placebo for 16 weeks (placebo group).[28] The primary outcome of the HS-PGA score was achieved by 17.6% of patients in the EW group, 9.6% in the EOW group, and 3.9% in the placebo group (difference: EW group vs placebo group, 13.7% [95% CI, 1.7%-25.7%], P = .02; EOW group vs placebo group, 5.6% [95% CI, 4.0%-15.3%], P = .25). Patients (n = 51) who had their adalimumab dose reduced from every week to every other week in the open-label extension phase after week 16 experienced a decrease in response from 17.6% to approximately 10%.[28]

Phase 3 adalimumab studies include the PIONEER I (n = 307) and PIONEER II (n = 326) studies. In both studies, patients were randomly assigned in a 1:1 ratio to receive 12 weeks of adalimumab or placebo in period 1. In the second study period (weeks 13-24), patients who received placebo in PIONEER I were reassigned to receive adalimumab weekly or they continued to receive placebo in PIONEER II in a blinded fashion. In both PIONEER I and II, patients who received adalimumab in the first treatment period were reassigned to receive adalimumab weekly, every other week, or placebo. The outcome for these studies was the HiSCR-50 with no increase in abscess or draining fistula count relative to baseline.[42]

In the PIONEER studies, significantly more patients receiving 40 mg of adalimumab every week than those receiving placebo achieved the HiSCR-50 primary outcome: 64 of 153 patients (41.8% [95% CI, 33.9%-50.1%]) taking adalimumab vs 40 of 154 patients (26.0% [95% CI, 19.2%-33.6%]) taking placebo in PIONEER I (P = .003); 96 of 163 patients (58.9% [95% CI, 50.9%-66.5%]) taking adalimumab vs 45 of 163 patients (27.6% [95% CI, 20.9%-35.1%]) taking placebo in PIONEER II (P < .001) (Table 2).[27,43]

Adverse events were comparable with other indications for adalimumab, and rates of serious adverse events were not statistically significant. During period 1 in PIONEER I, the rate of any adverse event was 50.3% in the adalimumab group and 58.6% in the placebo group. Serious adverse events rate was 1.3% in the adalimumab group and 1.3% in the placebo group. During period 1 in PIONEER II, the rate of any adverse event was 57.1% in the adalimumab group and 63.2% in the placebo group. The rate of serious adverse events was 1.8% in the adalimumab group and 3.7% in the placebo group.

Although these results are encouraging, the failure of treatment was common in both PIONEER studies (PIONEER I treatment group : period 1 [8 of 153 patients], 5.2% [95% CI, 2.3%-10.0%]; period 2 [41 of 96 patients], 4.2% [95% CI, 1.1%-10.3%]; PIONEER II treatment group: period 1 [8 of 163 patients], 4.9% [95% CI, 2.1%-9.4%]); period 2 [51 of 104 patients], 49.0% [95% CI, 39.1%-59.0%]).

Anakinra

Anakinra is a recombinant IL-1 receptor antagonist that inhibits binding of both IL-1α and IL-1β to IL-1 receptors, which are expressed by a wide range of cells including macrophages and T cells.[31] IL-1 levels are elevated in HS lesions and in perilesional skin.[31] In an RCT of 20 patients, a dosage of subcutaneous anakinra (100 mg once daily) was compared with placebo for 12 weeks, followed by 12 weeks of untreated observation.[31] At week 12 (end of the first period), HiSCR-50 was achieved by 3 of 10 (30.0% [95% CI, 7.0%-65.0%]) of the placebo group and in 7 of 9 (78.0% [95% CI, 40.0%-97.0%]) of the anakinra group (P = .04). No significant difference was found at week 24: 3 of 9 patients (33.3% [95% CI, 7.5%-70.1%]) randomized to placebo vs 1 of 10 patients (10.0% [95% CI, 0.3%-44.5%]) randomized to anakinra). This small study with modest results and incomplete follow-up yielded promising, but not definitive, results.

Ustekinumab

Ustekinumab is a human IgG1κ monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23, blocking the IL-12Rb1 receptor protein of natural killer cells and T cells.[30,44,45] Specific genetic variations of the gene coding for a subunit of the IL-12 and IL-23 receptor have been shown to be associated with a more severe course of HS.[30,45]

A prospective, uncontrolled, open-label study in HS among 17 patients receiving weight-based ustekinumab treatment (≤100 kg: 45 mg; >100 kg: 90 mg) at baseline and weeks 4, 16, and 28 with follow-up at week 40 has been conducted. Only 12 of 17 patients (70%) completed the study, 8 of 17 patients (47.0% [95% CI, 23.0%-72.2%]) achieved HiSCR-50, and 14 of 17 patients (82.0% [95% CI, 56.6%-96.2%]) had a moderate to marked improvement of the mSS at week 40. The mean mSS was significantly reduced from 112.12 at baseline to 60.18 at week 40 (46.33% improvement; P < .01 [95% CIs were not available]). The most common mild and temporary adverse events were headache, fatigue, and upper respiratory tract infections. One patient dropped out due to urticaria.[30]

Surgery

Surgery is required to definitively treat the tunnels and scars associated with chronic HS. Although surgery is commonly recommended, the literature supporting surgical treatment is anecdotal,

composed mostly of large case series or retrospective study reports (**Table 3**).[65] A systematic review by Mehdizadeh et al[66] concluded that a lower recurrence rate was found in procedures with wide excision (overall, 13%; primary closure, 15%; using flaps, 8%; grafting, 6%) compared with local excision (22.0%) or deroofing (27.0%). These operations can be disfiguring and despite the removal of significant amounts of tissue, do not necessarily protect against disease recurrence.

Incision and Drainage

Incision and drainage results in immediate pain relief when fluctuant abscesses are present, but should not be performed to treat solid, inflamed nodules because they do not have anything to drain.[67] Recurrence rates are high and the procedures are costly.[51,67,68]

Localized Excision or Tissue-Saving Methods

Local excision or tissue-saving methods like deroofing and skin tissue–saving excision with electrosurgical peeling (STEEP) have recently been assessed. In deroofing, a probe is used to explore tunnels (sinus tracts) and only the "roof" is excised, leaving the epithelialized floor of the sinus tract intact. In STEEP, diseased tissues are removed by stepwise tangential excisions, preserving unaffected tissue. In both methods, the wounds are left open to heal by secondary intention.[46,67] Postsurgical morbidity and the risk of scar contractures are reduced but recurrence rates are higher than for wide excision procedures (Table 3).

Wide Excision

Wide excision is defined as an excision of a lesion including a lateral margin of disease-free tissue, sometimes encompassing the entire anatomical region (eg, all axillary skin). It is associated with lower recurrence rates but greater postoperative morbidity (such as infection, bleeding, and contractures) (Table 3). Large wounds resulting from wide excision procedures are generally closed using split-thickness skin grafts or flaps, but are sometimes left to heal by secondary intention.[51,53,54,56,57,59,62] This results in a prolonged recovery and scar formation. Extensive surgery is necessary when the HS is complicated by the presence of cancer (eg, Marjolin ulcers) or amyloidosis secondary to the chronic inflammation (when amyloid [an acute phase protein] is deposited in, for example, the kidneys causing life-threatening nephrotic syndrome).[69-71]

Multimodal Therapy

In studies of adalimumab,[72-74] morbid obesity (defined as a body mass index [BMI; calculated as weight in kilograms divided by height in meters squared] greater than 40 was associated with less responsiveness to weekly adalimumab therapy and weight loss, increases spontaneous remission rates, and fewer recurrences after surgery.

Medical treatment can also be combined with surgery. A retrospective study of patients undergoing both surgery and biological treatment compared with surgery alone found significantly lower recurrence rates in previously treated sites (13.8% [95% CI, 3.9%-31.7%] for surgery + biological treatment [4 of 29 sites] vs 38.5% [95% CI, 20.2%-59.4%] for surgery alone [10 of 26 sites], $P < .01$) and less disease progression for those who continued biologic therapy for at least 6 months (18% for surgery + biologic treatment vs 50% for surgery alone). For patients in the surgery + biological treatment group, the disease-free interval between wound closure at the surgical site was 18.5 months (range, 4.0-30.0) and for the surgery alone group it was 6 months (range, 1.5-15.0) ($P < .001$).[63]

In a retrospective study of 30 patients with HS, the association of adding surgery to anti-TNF treatment was reviewed. Patients received infliximab for a mean of 9.3 months (range, 0.5-40.0), and 24 of 30 patients (80%) had surgery to remove remaining sinuses and fistulas not responding to the anti-inflammatory treatment (with an average of 2.8 procedures per patient including deroofing and large excisions). Outcomes were assessed with a 4-point HS-PGA scale (score range: 1 [no improvement], 2 [moderate improvement], 3 [improvement], 4 [free of lesions]).[64]

The mean patient score was 2.8 after infliximab monotherapy and 3.3 after adding surgery ($P < .001$; 95% CIs were not available). Six patients (20%) were treated with infliximab only (surgery was not necessary in 4 patients and 2 patients declined surgery). At the end of the follow-up period (mean, 50 months [maximum, 127 months]), 10 of 30 patients (33.0% [95% CI, 17.3%-52.8%]) were free of lesions, 13 of 30 patients (43.0% [95% CI, 25.5%-62.6%]) were improved, 4 of 30 patients (13.0% [95% CI, 3.8%-30.7%]) moderately improved, and 3 of 30 patients (10.0% [95% CI, 2.1%-26.5%]) had severe HS. Adverse events (not specified in the article) due to infliximab treatment were seen in 12 of 30 patients (40.0% [95% CI, 22.7%-59.4%]), resulting in treatment discontinuation in 9 of 30 patients (30.0% [95% CI, 14.7%-49.4%]). No surgical complications were observed.[64]

How to Manage Hidradenitis Suppurativa?

Apart from the new monoclonal antibody therapies, there is little high-quality evidence to support treatment recommendations for HS. Even the evidence regarding monoclonal antibody therapies are limited because they were compared only with placebo and not to treatments that are currently used to treat hidradenitis suppurativa. The following treatment recommendations are based on expert opinion and review of the available literature (**Figure 4**).

Medical

HS is a multifocal disease requiring systemic therapy, the choice of therapy is guided by disease severity. Based on the available evidence, 2 medical therapies can be recommended for mild disease: topical clindamycin (GRADE B; supported by a small RCT) and resorcinol (GRADE C). There is no available data to guide the choice between the 2, but the irritant effect of resorcinol makes it more suitable for use in smaller areas (eg, when only a few lesions are present). For mild or moderate disease unresponsive to topical treatment, tetracycline (500 mg twice daily; GRADE B) or doxycycline/minocycline (50-100 mg twice daily; GRADE D) can be administered. For moderate or severe disease, rifampicin (300 mg twice daily) and clindamycin (300 mg twice daily; GRADE B) may induce temporary remission. Initial treatments are usually begun with tetracycline-type drugs because they are less susceptible to developing resistant organisms and have more limited use as antibiotics.[37] Patients with moderate to severe disease

Table 3. Surgical Treatment Studies About Hidradenitis Suppurativa (HS) Published in the Last 5 Years

Reference	Method	Study Type (Evidence Level)	No. of Patients/ No. of Operations	Hurley Stage (% of Patients)	Anatomical Location	Relapse Rate, %	Follow-up	Complications, %	Comments
Blok et al[46]	STEEP or deroofing	Clinical records-based retrospective analysis (low)	113/482 (363 primary operations and 119 reoperations)	I (11.5), II (77.9), and III (10.6)	Armpit, groin, genital, buttocks, submammary, abdominal folds, and retroauricular and neck	Primary operations, 29.2	9-93 mo	Overall, 16; hypergranulation, 7.2; wound infections, 1.8; postoperative bleeding, 1.8	Indication for deroofing: Hurley stage I or limited stage II; indication for STEEP: extensive Hurley stage II and III
Janse et al[47]	STEEP	Prospective study of all consecutive patients (low)	16/27	II (50) and III (50)	Axillae, groin, buttocks, neck	50	Mean, 8.26 mo	Hypergranulation, 62.4 (most common)	
Posch et al[48]	Wide local excision followed by secondary healing	Retrospective study of consecutive patients (low)	74/NA	III (100)	Groin, genital, or gluteal (51 patients, 68.9%); axillae (23 patients, 31%)	local recurrence, 18.9 (14 patients): axillary, 1.4 (1 patient); groin, genital, or gluteal, 14.9 (11 patients); both, 2.7 (2 patients)	<1 y (78% of patients); mean, 4.72 y	Postoperative complications, 47.3 (35 patients); pain (30 patients), scarring (22 patients; of these, 7 had restrictions in mobility, 1 keloid), wound-healing deficiencies (4 patients), and infections (3 patients)	
Romanowski et al[49]	Two-stage approach: (1) removal of hair bearing skin, (2) slit-thickness skin graft	Retrospective study of consecutive patients (low)	98/212 (142 grafting procedures and 70 bilateral)	I (1), II (17.2), and III (79.8)	Lesions sites: Axilla (74), groin (43), trunk (20), perineum (19), pubic area (19), buttock (15), head (2), neck (3)	graft failure ≥30%, 18 (18 patients); regraft needed, 9 (9 patients)	1 y	NA	At 30 d after the initial procedure, 94.7% of all wounds were fully grafted and closed
Wollina et al[50]	Wide excision	Retrospective study (low)	117/NA	III (100)	Anogenital	Overall, 9.4 (11 of 117 patients); primary closure, 3.4 (4 of 117 patients); healing by secondary intension, 5.1 (6 of 117 patients	NA; review of patients receiving an operation from year 2000 to 2015	Overall, 20.5 (24 of 117 patients); patients: bleeding (3), postsurgical anemia (3), suture dehiscence (3), abscess (8), infection (1), erysipelas (1), scar contracture (1), developed appendicitis (1), pilonidal sinus (1), perforated colitis (1), colostomy (1)	Colostomy was needed in 1 patient
Kohorst et al[51]	Excision; deroofing, exteriorization, and curettage; or incision and drainage	Retrospective review (low)	590/590 (405 excisions [68.6%]; 168 deroofing, exteriorization, and curettage [28.5%]; and 17 incision and drainage [2.9%])	I (5.4), II (13.9), and III (80.7)	294 Perianal or perineal only (49.8%); 124 axillae only (21.0%); 76 gluteal only (12.9%); 12 inframammary only (2.0%); 84 two or more areas (14.2%)	Total, 24.4; required reoperation, 11.7	1-6961 d; mean, 632.9 d	Overall, 2.5; cellulitis, skin graft losses, wound dehiscence, hematoma, neuropathic pain, and retained foreign body	Closure type: primary layered closure, 246 patients (41.7%); healing by second intention, 250 patients (42.4%); closed by marsupialization, 47 patients (8.0%); closed by skin grafting, 29 patients (4.9%); closed by flap, 13 patients (2.2%) Conclusion: Incision and drainage had a markedly higher recurrence risk than those with surgical excision; patients with deroofing had recurrence risk similar to that for patients with surgical excision
Van Rappard et al[52]	Local excisions with primary closure	Retrospective review (low)	57/92	I and II	46 excisions in the inguinal-genital area (50%); 34 excisions in the axillae (37%); 8 excisions in the perianal area (9%); 4 excisions in other areas (4%)	Total, 34; within the operated fields, 23; de novo, 11	3 mo-5 y	Infection, 5 (5 patients); bleeding, 8 (7 patients); dehiscence, 22 (20 patients)	

(continued)

Table 3. Surgical Treatment Studies About Hidradenitis Suppurativa (HS) Published in the Last 5 Years (continued)

Reference	Method	Study Type (Evidence Level)	No. of Patients/ No. of Operations	Hurley Stage (% of Patients)	Anatomical Location	Relapse Rate, %	Follow-up	Complications, %	Comments
Humphries et al[53]	Wide excision and healing by secondary intention	Retrospective case review (very low)	17/23	NA	Excisions: 15 axillae, 2 breast, 14 groins; 5 perineum; 5 mons pubis or supra pubis; 1 presacral; 5 perianal; 3 abdomen; 2 inner thighs; 2 gluteal areas	11.7	Mean, 1.02 y	Lower-extremity DVT (1 patient); severe nausea or vomiting (2 patients); dysthymia (1 patient); blood transfusions (2 patients); polyarthralgia (1 patient)	Wounds were dressed with topical antimicrobial medication; wound healing time: 8 wk to 16 mo
Maeda et al[54]	Skin-graft technique	Retrospective review (very low)	18/18	I (27.8), II (66.7), and III (5.6)	Gluteal region	0	Mean, 61.3 mo (range, 17-113)	NA	
Schmidt et al[55]	Islanded posterior arm flap for regional reconstruction around the axilla	Retrospective review (very low)	20/31 (posterior arm flaps)	NA	Axillae	NR	NA	Minor wound healing disturbance (4 of 31 anatomical sites); anatomical sites: additional V-Y advancement flap (2); tip necrosis (1); wound infection with partial wound dehiscence (1)	The donor site scar will be visible on the posterior upper arm
Alharbi et al[56]	Wide surgical excision	Retrospective review (very low)	32/50	II and III	23 axillae sites; 17 inguinal sites; 8 perianal/perineal sites; 1 gluteal site; 1 trunk site	Recurrence, 18.75 (6 patients)	Mean, 24 mo	NA	Recurrence rate was seen in 6 patients with Hurley stage III and 5 of these were smokers (83.3%)
Wormald et al[57]	TDAP vs SSG	Prospective study of all consecutive patients (low)	27/27 (12 SSG or TDAP and 15 flap reconstruction)	III	Axillae	1/15 (TDAP group)	3, 6, and 12 mo after surgery	SSG group: delayed wound healing secondary due to partial graft failure (5 patients; 25%-65% graft loss); delayed wound healing at the donor site (1 patient); scar contraction (3 patients) TDAP group: debulking (1 patient); axillary scar revision (1 patient); donor site wound dehiscence and secondary cellulitis (1 patient)	All patients experienced reduction in pain or discomfort; TDAP group had faster recovery, fewer complications, fewer overall No. of procedures, and improved quality of life than the SSG group
Yamashita et al[58]	Two-stage surgery for HS: (1) staged artificial dermis and (2) skin grafting	Case series (very low)	18/33 (33 lesions)	II and III	Right buttock and perianal region	In terms of patients, 5.6; in terms of lesions, 3	Mean, 12.3 mo (range, 8-36)	Local infection after the first operation, 45 (15 of 33 lesions; 10 patients); minor skin graft loss, 3 (1 of 33 lesions)	
Alharbi et al[59]	Inner arm perforator flap in the management of axillary HS	Case series (very low)	10/12	NA	Axillae	0	Mean, 13 mo (range, 6-21)	Delayed wound healing (3 patients)	
Mutaf et al[60]	Triangular closure technique	Case series (very low)	16/NA (16 lesions)	NA (state extensive HS)	Sacrococcygeal	0	36 mo (6-5 y)	Tip necrosis (2 patients)	

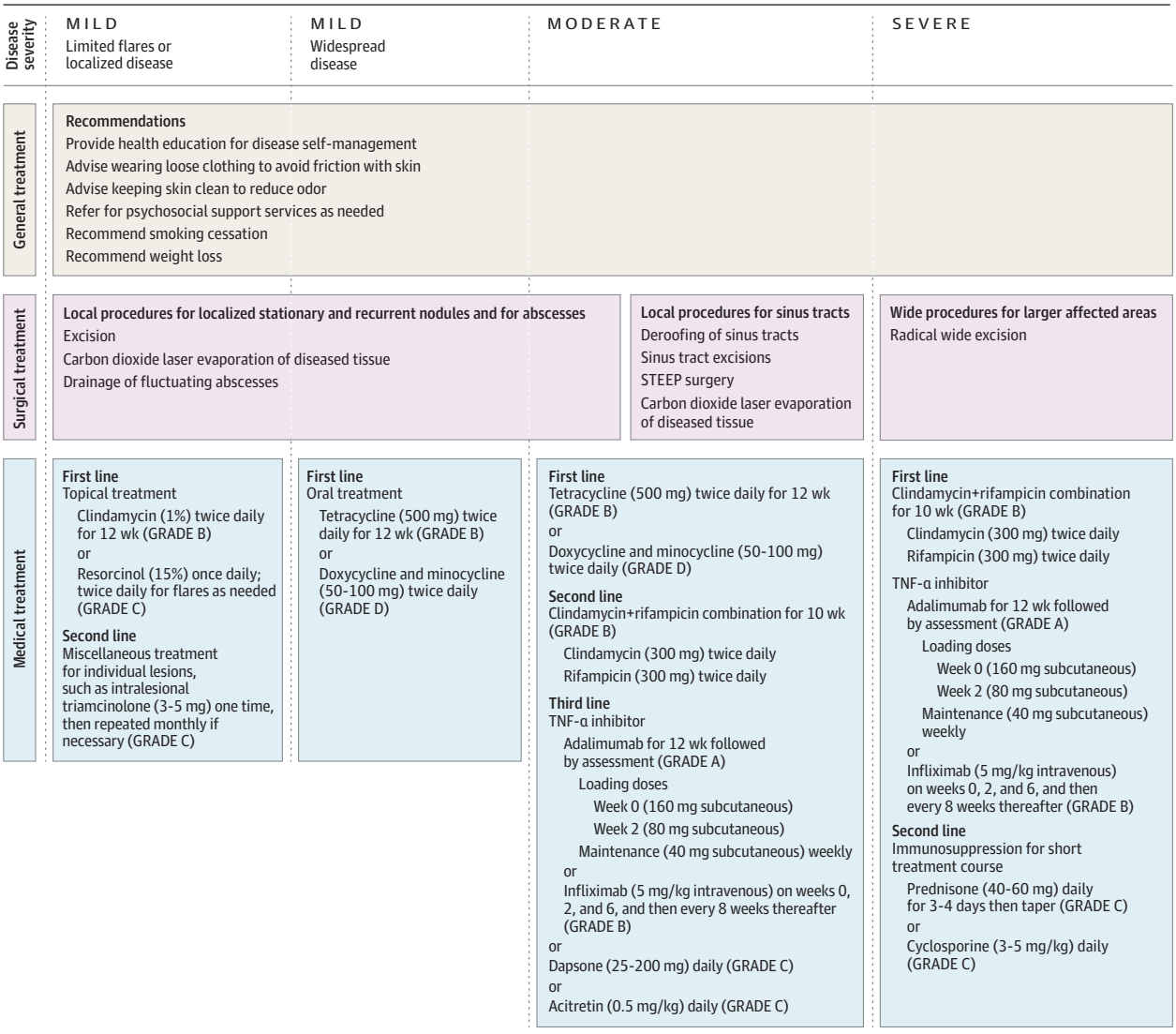
(continued)

Table 3. Surgical Treatment Studies About Hidradenitis Suppurativa (HS) Published in the Last 5 Years (continued)

Reference	Method	Study Type (Evidence Level)	No. of Patients/ No. of Operations	Hurley Stage (% of Patients)	Anatomical Location	Relapse Rate, %	Follow-up	Complications, %	Comments
Nesmith et al[61]	Radical surgical resection combined with lymphadenectomy-directed antimicrobial therapy	Retrospective review (very low)	11/15 (wide en bloc resections)	NA	Axillae	0	Mean, 4.3 y	No wound complications or disease recurrences	Empirical antimicrobial treatment of amoxicillin clavulanate or levofloxacin (if penicillin allergic) or adjustment after culture; no patients developed lymphedema or loss of function in the involved upper extremity
Wollina et al[62]	Primary closure (n = 25); delayed split-skin mesh-graft transplantation (n = 9); healing by secondary intention (n = 33)	Retrospective review (low)	67/NA	III (100)	Anogenital	6	Mean, 56.9 mo (SD, 41.3)	Total, 10.4 (7 patients); postoperative bleeding (1 patient); fever (1 patient); erysipelas (1 patient)	Mean HS-PGA score improved from 6.8 (SD, 1.2) to 0.9 (SD, 0.6); mean PaGa score improved from 7.3 (SD, 1.2) to 1.1 (SD, 0.5); mean HS-LASI score decreased from 41.8 (SD, 21.3) to 2.4 (SD, 2.8)
DeFazio et al[63]	Radical resection with delayed primary closure alone, or in combination with adjuvant biologic therapy.	Retrospective review (low)	21/21 (57 HS locations) (10 operations alone; 11 operations in combination with adjuvant biologic therapy [8 with infliximab and 3 with ustekinumab])	III (100)	Operations in combination treatment: 12 axillae (41%); 6 inguinal fold (21%); 5 groin/genital/perineal (17%); 4 breast (14%); 2 other (7%; trunk, neck, gluteal cleft) Operations in surgery alone: 13 axillae (50%); 2 inguinal fold (8%); 6 groin/genital/perineal (23%); 2 breast (8%); 3 other (11%; trunk, neck, gluteal cleft)	Recurrence, 19 (4/29 anatomical regions); previously treated sites for combined and surgery-only patients, 38.5 (10/26 anatomical regions) ($P < .01$)	Mean (range) Combination: 18 (6-31) Surgery alone: 20.5 (4-36)	Combination treatment: delayed wound healing (2 patients) Surgery alone: wound dehiscence (1 patient); surgical site infection (2 patients)	
Van Rappard et al[64]	Deroofing and small to large excisions, followed by healing by secondary intention, primary closure or grafting procedures	Retrospective study (low)	30/24 (24 operations and infliximab [80%]); 6 only infliximab [20%])	II (13) and III (87)	NA	NA for surgery	Mean, 50 mo (maximum, 127 mo)	Complications of surgery during or shortly after treatment with infliximab were not observed	Combination treatment: healed (37%), improved (53%); moderately improved (10%); no change (0%) Infliximab only: healed (13%); improved (61%); moderately improved (23%); no change (3%)

Abbreviations: DVT, deep venous thrombosis; GI, gastrointestinal; HiSCR-50, hidradenitis suppurativa clinical response 50%; HS-LASI, Hidradenitis Suppurativa Lesion, Area, and Severity Index; NA, not available; NR, none reported; PaGa, Patient Global Assessment; HS-PGA, Hidradenitis Suppurativa-Physician's Global Assessment; RCT, randomized controlled trial; SSG, split skin graft; STEEP, skin tissue–sparing excision with electrosurgical peeling; TDAP, thoracodorsal artery perforator flap; VAS, visual analog scale.

Figure 4. Suggested Algorithm for Treatment of Hidradenitis Suppurativa



GRADE indicates Grading of Recommendations Assessment, Development, and Evaluation. GRADE levels of evidence: A, high; B, moderate; C, low; D, very low. In principle, all patients should be offered general measures, medical treatment, and surgery in parallel and not sequentially. Mild but widespread disease generally does not provide a target for lesion-directed treatment; therefore, it is less suitable for surgery as the only category.

can also be treated with TNF antibody therapy, especially if they have required long-term antibiotic treatments for disease control, flared rapidly when antibiotic treatments were stopped, or have moderate to severe disease without secondary bacterial infections. Adalimumab was approved for the treatment of HS by the US Food and Drug Administration in 2016 (GRADE A). Infliximab may be used as an alternative anti-TNF therapy (GRADE B). In case of treatment failure, third-line treatment targeting IL-1 (anakinra; GRADE B), p40 (ustekinumab, GRADE C), dapsone (GRADE C), or acitretin (GRADE C) may be tried.

Surgical

Mild cases of HS can often be managed by intralesional administration of 3 mg to 5 mg of triamcinolone (GRADE C), but once chronic lesions form, surgery is necessary. For mild to moderate HS, carbon dioxide laser evaporation of lesions or deroofing or STEEP may be performed. Deroofing or STEEP may be tried when tunnels or cysts are present. Wide excision has a better cure rate than these operations, but may also be associated with a higher risk of complications, so it is reasonable to consider a stepwise approach escalating from least-invasive to more-invasive surgical options.

For moderate to severe HS, surgical wide excision is recommended in combination with medical and adjuvant therapy (Table 3).

Conclusions

Hidradenitis suppurativa is more common than previously thought and may be treated by an array of pharmacological and surgical techniques. Hidradenitis suppurativa should be considered in the differential diagnosis of nodular lesions or sinus tracts present in the axillae, groin, perineal, and mammillary fold regions.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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