Biologic and Systemic Agents in Hidradenitis Suppurativa

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Abbreviations

HiSCR	Hidradenitis suppurativa clinical response
HS	Hidradenitis suppurativa
HSS	Hidradenitis suppurativa score
STEEP	Skin-tissue-saving excision with electrosurgical peeling

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disease, typically localizing to the axilla, groin, or inframammary regions, characterized by recurrent nodules or abscesses, carrying the risk of scarring or sinus tract formation [1]. Despite the pain and potentially severe impact on quality of life from HS, and despite the fact that it is not rare, with a recent population-based survey reporting a prevalence of 2.10% in Denmark [2], HS has not attracted the same level of investigational attention as other dermatologic diseases such as acne or psoriasis. Consequently, a limited understanding exists about basic questions concerning HS pathogenesis, epidemiology, natural history, comorbidities, and effectiveness and safety of treatments. The latter limitation frequently obliges clinicians caring for HS patients to choose therapies that lack a robust evidence base; though more than 50 types of HS treatment have been described, there are few randomized controlled studies in HS providing high-quality evidence [3, 4]. This chapter evaluates the evidence for the efficacy and safety of commonly used and promising new systemic therapies for HS. It is intended to be more comprehensive than a meta-analysis of randomized controlled trials in HS [3], because so many commonly used therapies have not been studied in randomized controlled trials. It is not intended to be a compendium of every described HS therapy, because many such therapies have only been described in case reports or very small case series that serve better to generate scientific hypotheses than to influence treatment decisions.

A rational evaluation of the systemic therapies for HS must begin by considering what is known or hypothesized about the pathogenesis of the disease, followed by considering the scientific rationale for the therapeutic options, and then evaluating the quality and quantity of evidence supporting the use of that therapy. The pathogenic trigger of the disease is hypothesized to be occlusion of the infundibulum by follicular keratinocytes, followed by rupture of the hair follicle wall. Leakage of the pilosebaceous unit contents, including commensal bacteria, into the dermis then initiates an intense foreign body-like reaction mediated by resident dermal immune cells secreting pro-inflammatory cytokines and chemokines, which help recruit and activate other arms of the immune system [5]. Blocking the different steps of this disease—via modifying keratinocyte maturation (retinoids) or sebaceous gland activity (retinoids or antiandrogens), via anti-inflammatory effects (antibiotics or immunosuppressants), or via direct alteration of the HS microbiome (antibiotics)—is the rationale for including these medication types in the HS therapeutic armamentarium.

Limitations in the quality of clinical evidence interfere with our ability to reliably assess the efficacy and safety of many therapies. Interpretation of uncontrolled studies is problematic because the few placebo-controlled trials in HS have revealed that approximately 25% of moderate to severe placebo-treated HS patients experience clinically relevant spontaneous improvement in their disease [6], and the placebo response for patients with mild HS is likely higher. This may be due to a true placebo response or due to selection bias: disease activity of many HS patients is volatile, perhaps more than in other dermatologic diseases, and HS patients may be more willing to enroll in clinical trials or start new investigational therapies when their disease activity is peaking.

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Table 36.1 Hurley stage classification for HS patients

Stage I	Abscess formation, single or multiple, without sinus tracts or scarring
Stage II	Recurrent abscesses with sinus tract formation or scarring
	Single or multiple, widely separated lesions
Stage III	Diffuse or near-diffuse involvement or multiple interconnected sinus tracts and abscesses across entire anatomic region

Modified from: Hurley H. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus. In: Roenigk RK and Roenigk HH Jr., editors. Dermatologic Surgery: Principles and Practice. New York: Marcel Dekker; 1989. pg. 631–643

As a result, patients' improvement from their "baseline" disease activity, assessed at the time of initiation of an investigational therapy, may represent random fluctuation back toward their typical disease activity. In studies or case series without a placebo group, it is not possible to determine reliably how much improvement is due to therapy and how much is due to spontaneous improvement, but a reasonable heuristic would be to judge a therapy effective if substantially more than 25% of patients with moderate to severe HS experience clinically relevant improvement. In studies using an unvalidated endpoint (i.e., an endpoint lacking evidence of reliability and of clinical relevance), the reported improvement may not be reproducible in clinical practice or may not be meaningful to patients. From studies with few subjects or with limited follow-up, it is not possible to reliably determine the incidence of serious but low probability or long-term adverse events.

The first attempt to categorize HS disease stage within each involved anatomic region was proposed by Hurley [7] (Table 36.1). By convention, a patient's overall Hurley stage corresponds to the Hurley stage of his or her most advanced anatomic region: if a patient has at least one anatomic region with Hurley stage III disease, he or she is a Hurley stage III patient. The Hurley staging system was originally intended to help physicians classify patients as candidates for medical therapy (Hurley stage I), limited surgical intervention (e.g., excision of a sinus tract) (Hurley stage II), or more extensive surgical intervention (e.g., *en bloc* excision of an entire anatomic region) (Hurley stage III). It is not practical to use Hurley staging to classify disease severity, which is determined by a constellation of factors in addition to sinus tract formation or scarring, such as number and severity of inflammatory lesions, pain, and impact of the disease on quality of life. Hurley stage I patients may have severe disease, and Hurley stage III patients with no active inflammation may have mild disease. It is also not practical to use Hurley staging to assess the efficacy of a systemic therapy because it is insufficiently dynamic: the presence and extent of scars and sinus tracts differentiate among the Hurley stages, but once scars or sinus tracts are formed, no systemic medical therapy can reasonably be expected to reverse or downgrade the Hurley stage.

Two HS-specific objective endpoints have been validated and are therefore potentially useful tools for evaluating systemic therapy efficacy: the hidradenitis suppurativa score (HSS) or Sartorius score, which has undergone modifications from its original iteration [8], and the hidradenitis suppurativa clinical response (HiSCR) [6]. The modified Sartorius score is a composite score comprising the number of involved anatomic regions, the numbers and types of lesions for each region, and the extent and severity of involvement within each region. Reproducibility and inter-rater reliability of the modified Sartorius score have been established. The modified Sartorius score suffers from a lack of definition of what constitutes clinically meaningful improvement and contains disparate elements that reflect disease activity (e.g., nodules) and also disease damage (e.g., Hurley stage). As medical therapies can be expected to reduce disease activity but not affect disease damage, change in the modified Sartorius score may not be optimally sensitive to detect clinically relevant improvement. HiSCR response is defined as at least a 50% reduction in total abscess and/or inflammatory nodule count, so long as the abscess count is not increased and the draining fistula count is not increased. Reproducibility and inter-rater reliability of HiSCR have also been established, and achievement of HiSCR response has been demonstrated to be clinically meaningful for patients [9]. US and European regulatory authorities recognize HiSCR as a valid endpoint, as it has been used successfully in phase III clinical trials to achieve regulatory approval of adalimumab for treatment of moderate to severe HS. HiSCR exclusively focuses on disease activity, with no assessment of disease damage included in the measure. In addition to these HS-specific objective endpoints, treatment response can be evaluated using subjective health-related quality of life measures, including validated dermatology-specific measures such as the dermatology life quality index (DLQI) and/or pain VAS scores.

Immunosuppressants

Overexpression of tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) in HS lesional tissue [10] provides the scientific rationale for targeting these pro-inflammatory cytokines. The cellular sources of TNF-α and IL-1β in lesional tissue are uncertain but may include monocytes and macrophages, which are abundantly present in HS lesions and may be activated by pro-inflammatory signals from keratins released followed follicular unit rupture, or from commensal bacteria.

TNF Antagonists

Numerous case reports and series describe the successful use of adalimumab, etanercept, and infliximab for treatment of HS, but an uncontrolled prospective open-label trial of etanercept at a dose of 50 mg weekly demonstrating a clinical response in 3 of 15 patients [11] led to etanercept falling into disfavor relative to other TNF antagonists.

Adalimumab

Adalimumab is a self-injectable monoclonal antibody specific for TNF-α. A phase II dose ranging trial [12] and two confirmatory phase III placebo-controlled trials [6] demonstrated that adalimumab was significantly effective for treatment of HS. The outcomes from these studies resulted in the approval of adalimumab for treatment of moderate to severe HS in the USA, Canada, and the EU, with a dosing regimen of 160 mg at week 0, 80 mg at week 2, and 40 mg weekly starting at week 4. Figure 36.1a, b depicts an affected crural fold before and after 6 months of therapy with adalimumab 40 mg weekly dosing.

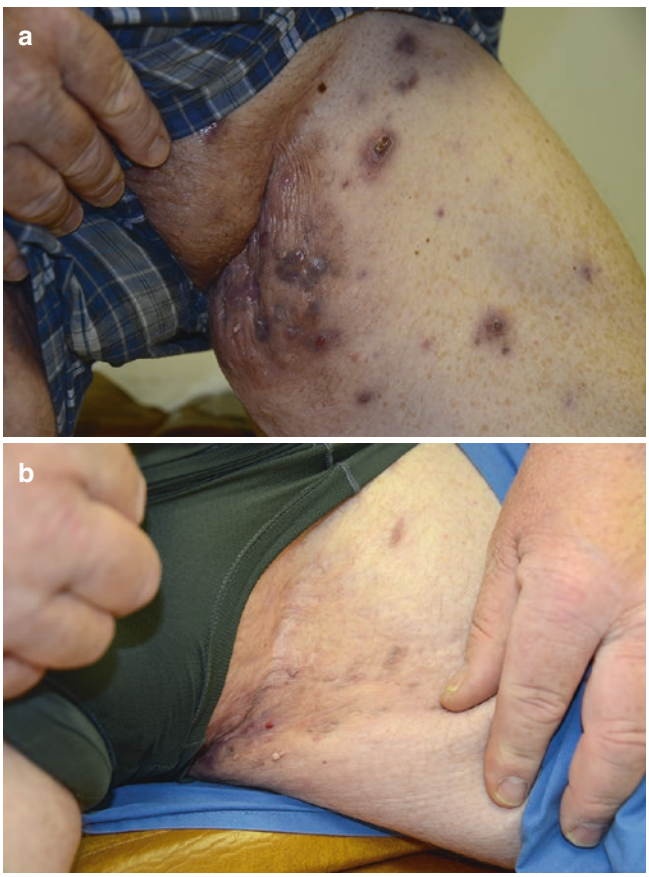

Fig. 36.1 Clinical photographs of the left groin of a patient with severe HS before (**a**) and after (**b**) six months of adalimumab 40 mg weekly dosing therapy. Clinical photographs are courtesy of Dr. Marc Bourcier, Moncton, New Brunswick, Canada

The two phase III trials, dubbed PIONEER I and II, randomized 633 patients to adalimumab or placebo. To enter these trials, patients were required to have failed oral antibiotic therapy, have Hurley stage II or III disease in at least one anatomic region, and have at least three abscesses or inflammatory nodules. PIONEER I patients were not allowed concomitant oral medications for treatment of HS; PIONEER II patients who were concomitantly taking a stable dose of minocycline or doxycycline for HS were permitted to continue these oral antibiotics but no other systemic HS therapies. Patients were randomized 1:1 in a double-blind manner either to adalimumab at the above dosing regimen or to placebo, with the validated HiSCR response rate measured at week 12 serving as the primary efficacy endpoint. At week 12, patients who had originally been randomized to adalimumab were rerandomized to continue adalimumab 40 mg weekly, or to receive adalimumab 40 mg every other week dosing, or to receive placebo, with the studies concluding at week 36.

In PIONEER I and II, week 12 HiSCR response rate was 41.8 and 58.9% for adalimumab-treated subjects versus 26.0 and 27.6% for placebo-treated subjects, corresponding to a significant treatment effect [difference in response between adalimumab- and placebo-treated subjects] of 15.8–31.3%. Compared to the treatment effect observed with adalimumab 40 mg every other week dosing in moderate to severe psoriasis patients, the treatment effect of adalimumab 40 mg weekly dosing in moderate to severe HS patients was smaller. The higher treatment effect noted in PIONEER II compared to PIONEER I was partially a consequence of the higher treatment effect in the stratum of patients receiving concomitant oral antibiotics (in PIONEER II, the treatment effect among patients receiving concomitant oral antibiotics for HS was 42.6% vs. 28.6% for patients not on concomitant oral antibiotics) and partially a consequence of milder baseline disease state in PIONEER II. In PIONEER I and II, mean improvements from baseline to week 12 in DLQI scores for adalimumab-treated patients (5.4, 5.1) exceeded the minimal clinically important difference in inflammatory skin diseases for DLQI of 4 [13] and were significantly better versus placebo-treated patients (2.9, 2.3) [$p < 0.001$ in both studies]. While the studies were inadequately powered to test statistical significance of the different dosing regimens from weeks 12 to 36, the numerical trend favored the weekly dosing treatment arm, corroborating the results from the adalimumab phase II dose ranging trial which demonstrated that 40 mg every other week dosing did not result in meaningful improvement above what was observed in placebo patients. The adalimumab safety profile across the phase II and III trials was consistent with what has been observed for adalimumab in clinical trials in other disease states, with no

notable increase in the frequency of serious infections among adalimumab-treated versus placebo-treated patients.

Infliximab

Infliximab is a monoclonal antibody specific for TNF-α administered by intravenous infusion. A double-blind phase II trial randomized 15 patients to receive infliximab at a dose of 5 mg per kg at weeks 0, 2, and 6 or 23 patients to placebo [14]. The primary efficacy endpoint was the percentage of patients achieving at least 50% improvement in the hidradenitis suppurativa severity index (HSSI), an unvalidated endpoint, at week 8. There was no significant difference in the primary efficacy endpoint between the infliximab and placebo arms. Post hoc analysis demonstrated that 60% of infliximab-treated patients achieved between 25 and 50% improvement in HSSI compared to 5.6% of placebo patients ($p < 0.001$). Mean change in DLQI for infliximab-treated patients was 10.0, compared with 1.6 for placebo-treated patients ($p = 0.003$). The observed adverse event profile was consistent with what would be expected in a population receiving infliximab infusions for other indications.

Anakinra

Anakinra is an antagonist to the interleukin-1 receptor, capable of binding to and blocking the biological activity of IL-1α and IL-1β. In a placebo-controlled double-blind trial of 20 subjects with Hurley stage II or III disease, subjects were randomized 1:1 in a double-blind manner to anakinra 100 mg administered subcutaneously or to placebo [15]. Anakinra therapy was associated with a significantly higher proportion of patients experiencing reduction from baseline in their disease activity score (determined by the size and degree of inflammation of the two largest lesions in each involved anatomic region) and a significantly higher HiSCR response rate (78% of anakinra-treated patients vs. 30% of placebo-treated patients). Adverse events reported in the anakinra group included diarrhea and vaginal candidiasis.

Ustekinumab

Ustekinumab is a monoclonal antibody approved for treatment of psoriasis that binds the p40 subunit common to il-12 and il-23. Based on evidence that the il-23 pathway is activated in HS, an open-label prospective trial in which 17 HS patients were treated with ustekinumab at the dosing regimen approved for psoriasis [16]. The week 40 HiSCR response was 47% (8 of 17 patients), and 41% of patients experienced a reduction in DLQI of at least 5 points. The HiSCR response rate was intermediate between reported from adalimumab treatment groups in PIONEER I (41.8%) and PIONEER II (58.9%) trials, but results from these trials cannot be compared directly because of notable differences in baseline demographics, with patients in the ustekinumab trial having substantially lower body mass index than patients in the PIONEER trials.

Antibiotics

Clindamycin and Rifampicin

The scientific rationale for treating HS with clindamycin and rifampin derives from their direct antimicrobial activity against *S. aureus*, coagulase-negative staphylococci, and anaerobic bacteria, which are occasionally cultured from HS lesions [17]. Using these antibiotics in combination reduces the risk of selecting for resistant organisms. Their mechanism of action in HS may not depend strictly upon their antimicrobial properties, as clindamycin modulates oxidative activity of mononuclear cells in a mouse model [18] and rifampin inhibits human neutrophil activity [19].

Three retrospective case series [20–22] and one prospective case series [23], which together report on the experiences of 141 patients, describe the efficacy and safety of combination clindamycin and rifampin in HS. The most commonly employed treatment regimen was a 10-week course of oral rifampin at a dose of 300 mg twice daily and oral clindamycin at a dose of 300 mg twice daily. Efficacy outcomes among the studies were variable, possibly related to differences in patient baseline characteristics or efficacy endpoints across the study populations, but between 56.5% and 85% of patients experienced clinically relevant improvement. Mendonça and Griffiths performed their retrospective analysis of 14 patients, 10 of whom entered "clinical remission" (not defined) after a 10-week treatment course, with remission duration of 1–4 years. All ten patients who experienced remission had disease in the perineal area at baseline, with some of these patients having disease in additional areas. Six patients could not tolerate clindamycin therapy due to the GI side effects of diarrhea: four discontinued the treatment regimen and two were switched to minocycline 100 mg per day. Van der Zee et al. performed their retrospective analysis on 34 patients, 23 of whom received clindamycin 300 mg po bid and rifampicin 300 mg po bid for different treatment durations. A physician's global assessment (PGA) was utilized to evaluate disease severity. Total remission was defined as more than 75% improvement in PGA relative to baseline. Most patients had Hurley stage II or III disease at baseline. Slightly more than half of patients (56.5%) treated with this regimen experienced total remission, and prolonging treatment duration beyond 10 weeks was not associated with

a meaningfully higher likelihood of remission. Total remission rates were higher for patients with Hurley stage II disease at baseline (60%) compared to patients with Hurley stage III disease at baseline (29%). Two-thirds of patients with total remission experienced relapse (not defined), with 5.0 months being the mean time to relapse for the relapsers. Approximately one-quarter (26%) of patients discontinued therapy due to side effects. In Gener et al.'s retrospective report on 116 HS patients treated for 10 weeks with clindamycin (300 mg po bid) and rifampin (600 mg po bid), for whom follow-up data on 70 patients were available, statistically significant improvement in Sartorius scores was noted, with median Sartorius score decreasing 50% (from 29 to 14.5). Pain and frequency of purulent drainage decreased significantly, and 66% of patients self-rated the result of treatment as "very good." Unfortunately, week 10 data was missing for 40% of the treated patients. Among the patients with available week 10 data, the discontinuation rate was 11.4%, mostly due to GI symptoms. The 23 HS patients treated prospectively by Bettoli et al. with combination clindamycin-rifampicin experienced a mean reduction in Sartorius score from 132.05 at baseline to 71.50 at week 10, corresponding to a mean decrease of 45.85%. The authors arbitrarily chose 25% improvement in Sartorius score as clinically meaningful; by this criterion, 85% of patients experienced clinically meaningful improvement. Three of 23 patients discontinued treatment, and 3 of 23 patients noted GI side effects. Shortcomings of these studies include absence of a placebo group, variable availability of follow-up data (with incomplete and limited follow-up for patients who experienced remission), and the use of endpoints that were either unvalidated or, in the case of Sartorius score, lacking a validated threshold for clinically meaningful improvement.

Other Antibiotics

Oral tetracycline (500 mg twice daily) was compared with topical clindamycin (1% lotion twice daily) in a double-blind, double-dummy 3-month randomized control trial of 46 Hurley stage I and II patients [24]. Compared to baseline, both treatment arms experienced significant improvement in a variety of efficacy measures. No significant differences were noted between the treatment arms, but the study did not provide power calculations, making it possible that the study lacked power to detect a significant difference. Based on the available data, it is not possible to determine the percentage of subjects who experienced clinically relevant improvement. At baseline, subjects had less than three abscesses and less than five nodules. In both treatment groups, median abscess count and nodule count were approximately halved after 3 months of treatment.

Based on a smaller case series describing successful treatment of HS with dapsone [25], outcomes from 24 HS patients treated with dapsone, at doses ranging from 50 to 200 mg per day for up to 48 months, were reported [26]. With 100% ascertainment at follow-up, "clinically significant improvement" (defined as "drastic relief and major clinical improvement") was observed in six patients (25%). One patient with clinically significant improvement experienced disease recurrence rapidly after treatment discontinuation, but responded again to dapsone when it was reinstituted, suggesting that the improvement observed with dapsone therapy was not coincidental. Two of 24 patients discontinued due to dapsone-related adverse events. The principal strength of this series is the complete ascertainment of treatment outcomes; weaknesses include absence of a placebo control group and lack of a validated endpoint. Interestingly, the reported rate of clinically significant improvement was not notably different from the placebo HiSCR response rate in adalimumab clinical trials (25.0–26.7%), suggesting that at least some of the patients experiencing clinically significant improvement may instead have been undergoing spontaneous, random fluctuation in disease activity.

In a retrospective study, 28 HS patients were treated with a combination of rifampin (10 mg per kg per day), moxifloxacin (400 mg per day), and metronidazole (500 mg tid), sometimes preceded by a 2-week course of intravenous ceftriaxone (1 g per day) and oral metronidazole (500 mg tid) [27]. Metronidazole was administered for 6 weeks, but rifampin and moxifloxacin were continued until disease remitted (i.e., inflammatory lesions were absent at two consecutive visits). Complete remission was achieved by 16 patients (57%), though most Hurley stage III patients failed to remit. Patients achieving complete remission were maintained on trimethoprim-sulfamethoxazole (400 mg/80 mg daily) or doxycycline (100 mg daily). Among the 14 patients who entered remission and had long-term follow-up, 7 experienced relapse. Nausea and diarrhea affected the majority of patients, and four experienced moxifloxacin-associated tendinitis necessitating treatment discontinuation.

In an improved treatment algorithm, 30 patients were treated with intravenous ertapenem (1 g daily) for 6 weeks, followed by the rifampin/moxifloxacin/metronidazole combination described above until disease remitted [28]. Sixteen patients adhered to this treatment regimen; their median Sartorius score decreased from 50.5 at baseline to 12.0 at month 6. Patient remission rates were not provided; remission rates by body region were 100% for Hurley stage I, 96% for Hurley stage II, and 27% for Hurley stage III. Most of the patients required repeat treatment to maintain disease control. During the ertapenem induction, oral and/or vaginal candidiasis was reported for 27% of ertapenem-treated patients, and one patient experienced lymphangitis.

Other Therapies

Zinc

Because zinc salts have been hypothesized to have anti-inflammatory properties and because efficacy with zinc gluconate in treatment of mild to moderate acne has been described, a pilot open-label study of zinc gluconate to treat predominantly Hurley stage I and II patients was conducted [29]. Subjects received 90 mg zinc gluconate per day, which was decreased by 15 mg every 2 months once complete remission (defined as resolution of inflammatory lesions or no new lesions for at least 6 months), or once partial remission (defined as at least 50% reduction in inflammatory lesions or a shorter duration for inflammatory lesions), had been achieved. Eight of 22 patients (36%) achieved complete remission, with the remaining patients achieving partial remission. Treatment was not remittive following dose reduction. One patient discontinued due to nausea and vomiting. Shortcomings of this study include absence of a placebo group, few subjects (one subject with Hurley stage III disease), ambiguity about follow-up duration and endpoint definition, and lack of information about efficacy for different Hurley stages. A subsequent open-label study of 66 patients treated with oral zinc gluconate combined with topical 2% triclosan reported improvements in median Sartorius and DLQI scores [30].

Hormonal Therapy

Clues pointing to a hormonal influence on HS pathogenesis include female preponderance, onset typically after puberty, rarity among postmenopausal women, reports of HS exacerbations associated with menses, and possible association with the hyperandrogenic state of polycystic ovary syndrome [31]. However, no consistent evidence of abnormal serum levels of sex hormones exists, though this does not preclude abnormalities in sex hormone metabolism peripherally, in hair follicles or sebaceous glands.

If hyperandrogenism can trigger HS, then antiandrogens are rational treatment options. Lee and Fischer [32] reported an uncontrolled retrospective analysis of 20 female patients treated with spironolactone 100 mg per day, using an unvalidated PGA scale modified from Kimball et al. [12] that classifies patients into grades of clear, mild, moderate, or severe based on counts of abscesses, draining fistulas, and inflammatory nodules. Response rate was 85% (17 of 20 patients experiencing at least 1 grade improvement relative to baseline); if more stringent response criteria are employed to assess outcomes (i.e., improvement by more than 1 grade relative to baseline), 7 of 12 moderate patients became clear and 1 of 3 severe patients became mild, for a response rate of 53% (8 of 15). Response was typically observed by month 5 or 6. No information was provided about whether any of these patients had clinical or biochemical evidence of hyperandrogenism prior to starting spironolactone. One patient discontinued treatment due to altered mood and dizziness. Shortcomings of this study include its retrospective nature, absence of a placebo control, and concomitant use of potentially beneficial medications (five patients were on concomitant minocycline and seven patients were on concomitant oral contraceptives). The antiandrogen cyproterone acetate (unavailable in the USA) combined with ethinyl estradiol was compared with norgestrel and ethinyl estradiol in a double-blind crossover trial of 24 female HS patients [33]. Both treatment regimens reduced disease activity comparably. Seven of 24 patients experienced disease clearance as assessed by physicians; by patient self-assessment, approximately twice as many patients experienced improvement compared to worsening with one of the regimens. The small number of enrolled patients, the high dropout rate (25%), and the absence of a placebo control limit the study's generalizability. Interestingly, in a case series of 29 patients treated with different types of antiandrogens, evidence of biochemical androgenism was not a factor predictive for responsiveness [31]. Finasteride was tested in seven male and female HS patients who had failed oral antibiotics [34], based on the hypothesis that hair follicle-mediated conversion of testosterone to dihydrotestosterone by type II 5α reductase drives HS pathogenesis. Three patients experienced no new lesions within 2–8 weeks of treatment initiation, and three had fewer or smaller lesions. The small size of this study limits its generalizability.

Metformin

Metformin is typically used for treatment of type II diabetes and polycystic ovary syndrome and reduces plasma glucose levels through a variety of mechanisms including reduced glucose production from hepatocytes, reduced intestinal absorption of glucose, and heightened insulin sensitivity. Its precise mechanism of action is unknown. As type II diabetes and polycystic ovary syndrome are common comorbidities in HS patients, Verdolini et al. [35] conducted an uncontrolled case series of 25 HS patients treated with metformin for 24 weeks. At doses up to 500 mg tid, 18 patients experienced an improvement in the Sartorius score relative to baseline, with 7 of these patients (28%) experiencing at least a 50% improvement in Sartorius score relative to baseline. If it is assumed, based on how the Sartorius score is derived, that a 50% improvement in Sartorius scale is the threshold for clinically meaningful improvement, then the 28% response rate is not markedly higher than the HiSCR placebo response rate of 25–27% reported by

Kimball et al. [6]. Assessment of plasma glucose levels was not performed in these patients, so it is unknown whether those patients with a clinically relevant response had elevated glucose levels prior to starting metformin or a marked reduction in their levels after starting metformin. Minor GI disturbances at the beginning of treatment were the only recorded side effects.

Systemic Retinoids

Systemic retinoids reduce epithelial proliferation, normalize differentiation, and are anti-inflammatory. Isotretinoin was first tested for efficacy in HS by Boer and van Gemert [36], who published retrospective results from 68 patients treated for 4–6 months with isotretinoin (mean daily dose of 0.56 mg per kg). Sixteen patients (23.5%) were "virtually clear" at the end of treatment, all of whom had mild or moderate HS at baseline. The authors concluded that isotretinoin had "limited value" in HS management. This study was followed by a retrospective series of 12 patients with Hurley stage II or III disease treated with acitretin at a mean dose of 0.59 mg per kg for 9–12 months [37]. Nine patients entered total remission, defined as at least 75% improvement in inflammation as measured with a physician's global assessment scale. All but one of the patients experienced clinically meaningful reduction in pain severity. Remission duration lasted between 6 and 45 months. The side effect profile was similar to what is seen for acitretin in psoriasis patients. Marked objective improvement observed in the majority of patients, coupled with substantial improvement in pain, must be tempered by the considerations that this was an uncontrolled retrospective study without a validated objective endpoint, and that acitretin is not practical to use in women of childbearing potential, who comprise the majority of HS patients.

Surgery

Surgical intervention is a complementary approach to managing HS, with potential advantages and disadvantages relative to medical therapy. Because sinus tracts are not expected to resolve with medical therapy, surgery is the only possible means by which these lesions can be definitively eliminated. Successful surgery may, by permanently removing skin prone to abscesses or inflammatory nodules, obviate the need for chronic medical therapy. Disadvantages of surgery are the postoperative morbidity, the risk of complications (e.g., wound infections or dehiscence, bleeding, and scarring limiting the range of motion), and the risk of recurrence (which is less acceptable than recurrence for patients who discontinue medical therapy because medical therapy is generally more tolerable). Surgical outcomes reported in case series or trials cannot be comprehensively evaluated unless the degree of postoperative morbidity; the risk, duration, and severity of surgical complications; and the risk of recurrence are included in the evaluation, and the risk of recurrence may be underestimated if follow-up duration is short.

Excision is the most commonly reported surgical technique employed to manage HS. After excision, surgical wounds may be closed primarily if they are relatively small or may be left to heal via secondary intention, flaps, or grafts if relatively large. Based on case series in which these different closure methods were employed, wounds that underwent primary closure had a higher recurrence risk, presumably because excisions small enough to undergo primary closure were too small to excise all diseased tissue (but to prove this presumption would require a study examining recurrence risk after mandating that methods other than primary closure be used for small wounds, which would be ethically ambiguous). Mandal and Watson [38] noted that among 100 of their patients treated with excision and primary closure, 70% had recurrences requiring additional surgery, but among 43 patients treated with excision and flap or graft, none experienced recurrence [38]. Median follow-up was 4 years; no information about the degree of postoperative pain or duration of postoperative recovery was provided. In a separate series of 31 patients treated with drainage, limited excision, or "radical wide excision" (defined as "all hair-bearing skin (with or without signs of HS) of the affected region with a clear margin of at least 1 cm"), recurrence rates requiring repeat surgery were 100%, 42.8%, and 27%, respectively (with a mean follow-up of 72 months) [39]. Further evidence about the potentially high risk of recurrence in HS wounds undergoing primary closure comes from a 200-patient placebo-controlled trial evaluating the efficacy and safety of placing a collagen matrix containing gentamicin (or placebo) in the wound bed of HS lesions excised and closed with primary intention healing [40]. Three-month recurrence rates were 40% in the gentamicin group and 42% in the control group. van Rappard et al.'s [41] recurrence rate following excision and primary closure was 23% (after a mean follow-up of 10 months). With recurrence rates following local excision and primary closure ranging from 23 to 70%, local cure with this approach is possible but unpredictable.

Larger-scale excisions can result in low recurrence rates, so long as diseased tissue is adequately removed and the surgeon and patient have the capability to manage wounds too large to undergo primary closure, and can manage and tolerate postoperative complications. Rompel and Petres [42] analyzed data from 106 of their HS patients who underwent excision after identification of all communicating branches of sinus tracts via intraoperative injection of methyl violet solution. Excision with this technique typically reached deep subcutaneous tissue or fascia. The different methods used for

closure (primary closure, secondary intention, flaps, or grafts) did not influence the risk of complications, which were low (e.g., wound infections were observed in 3.7% of patients). The recurrence rate across the different closure methods was also low at 2.5%, with a median follow-up of 36 months. No information was provided about the extent or duration of postoperative morbidity such as time to wound healing, nor was recurrence defined. Similarly, among another set of 57 HS patients who underwent excision, followed either by primary closure, secondary intention healing, or skin grafting, no local recurrences were noted after a follow-up of 8.4–21.2 months [43]. Postoperative morbidity was not reported. Bohn and Svensson [44] summarized their experiences with 116 HS patients who received excisions extending down to fascia and out to 2 cm beyond the margin of clinically involved skin. Most patients needed split skin grafting. With an 8-year median postoperative follow-up, no patient experienced a relapse in the grafted sites. Anesthesia or paresthesia lasting longer than 3 months was common, and seven patients had limited range of motion of their shoulder persisting up to 5 months. Not all surgical series reporting on excisions replicated such good outcomes: complete clearance was noted in only 59.7% of 57 HS patients who underwent excision in one series [45] and Ritz et al.'s 27% recurrence risk with "radical wide excision" is noted above. Other than closure type (functioning as a proxy for wound size), factors reported to affect recurrence risk include location (axillary and perianal HS less likely to recur compared to inguinal or genital HS) [39] and female gender [46].

Surgical techniques other than scalpel excision have also been described. The STEEP technique ("skin-tissue-saving excision with electrosurgical peeling") is a series of tangential passes designed to progressively remove exclusively diseased tissue with electrosurgery. Blok et al. [46] report a recurrence rate of 29.2% and a wound infection rate of 1.8% after 482 operations and a median follow-up of 43 months [46].

For isolated, chronic lesions in patients with Hurley stage I or II disease, deroofing is a tissue-saving alternative to radical wide excision, as reported by van der Zee et al. [47]. Under local anesthesia, sinus tracts were delineated with a blunt probe, and the skin overlying the sinus tracts was removed with scalpel or electrosurgery. Debris within the sinus tracts was curetted, and the defect was allowed to heal via secondary intention. No recurrence was noted in 83% of the 88 treated lesions, with a median follow-up of 34 months. Mean healing time was 14 days.

The long-pulsed 1064 nm Nd:YAG laser has demonstrated significant efficacy in a prospective trial of patients with multiple involved anatomic regions, who had 4 monthly laser or control treatments randomized to different regions within the same patient [48]. Its mechanism of action in HS is unknown. For regions receiving laser therapy, the entire anatomic region was treated with a single pulse and inflammatory lesions received double pulses. One month after the last laser treatment, percentage improvement in modified Sartorius score among laser-treated regions was 63.6%, compared to 5.3% for control regions ($p < 0.001$). Seventeen of 22 patients (77%) completed all 4 treatments, and treated inflammatory lesions healed within 2–7 days. Recurrence rate after laser therapy completion was not studied.

Ablation of diseased tissue with a CO_2 laser is a relatively bloodless and tissue-sparing alternative to scalpel excision [49]. In this case series, ablation was performed in stages on 24 Hurley stage II patients, with the procedure repeated until all tissue not identified as normal subcutaneous fat was removed. Recurrence rate was 8% (2 of 24 treated sites) over a mean follow-up period of 24 months. Despite generating wound areas of 6–40 cm^2, postoperative pain requiring analgesics lasted no more than 4 days and most patients could resume daily activities within 3 weeks. The same group later improved upon this technique by using a scanner-assisted CO_2 laser, which automatically varies the direction of the laser beam and thereby makes the ablation less operator-dependent than the prior "freehand" method [50]. For more severely affected patients (Hurley stage III), CO_2 laser therapy to excise diseased tissue in cutting mode has been described in a retrospective case series of nine patients with 1-year follow-up [51]. Depending upon defect size, wounds underwent primary closure or secondary intention healing. One patient developed a local recurrence, and one developed postoperative wound dehiscence. A subsequent 61-patient series also reported low incidence of recurrence (with 2 patients experiencing recurrence at the edges of laser-treated areas) and low incidence of complications (3 postoperative cellulitis cases). Wounds averaged approximately 2 months to heal by secondary intention. Compared to scalpel excisions, CO_2 laser therapy is relatively bloodless, making it technically easier to visualize and eradicate subcutaneous sinus tracts. While these reports are promising, small patient numbers and follow-up limit inferences about long-term effectiveness and safety, and few surgeons have the equipment, expertise, or interest to perform CO_2 laser surgery on HS lesions.

Conclusions

Gulliver et al. have proposed an evidence-based approach to HS management (Fig. 36.2) [52]. Recommended first-line therapy for mild disease is twice daily topical clindamycin 1% lotion. For more widespread or severe disease, oral therapy is advised: tetracycline 500 mg twice daily for at least 4 months or, in case of more severe or recalcitrant disease, a 10-week course of clindamycin 300 mg twice daily and rifampin 600 mg once daily. For patients with an inadequate response to oral antibiotics, adalimumab at the HS-approved dose

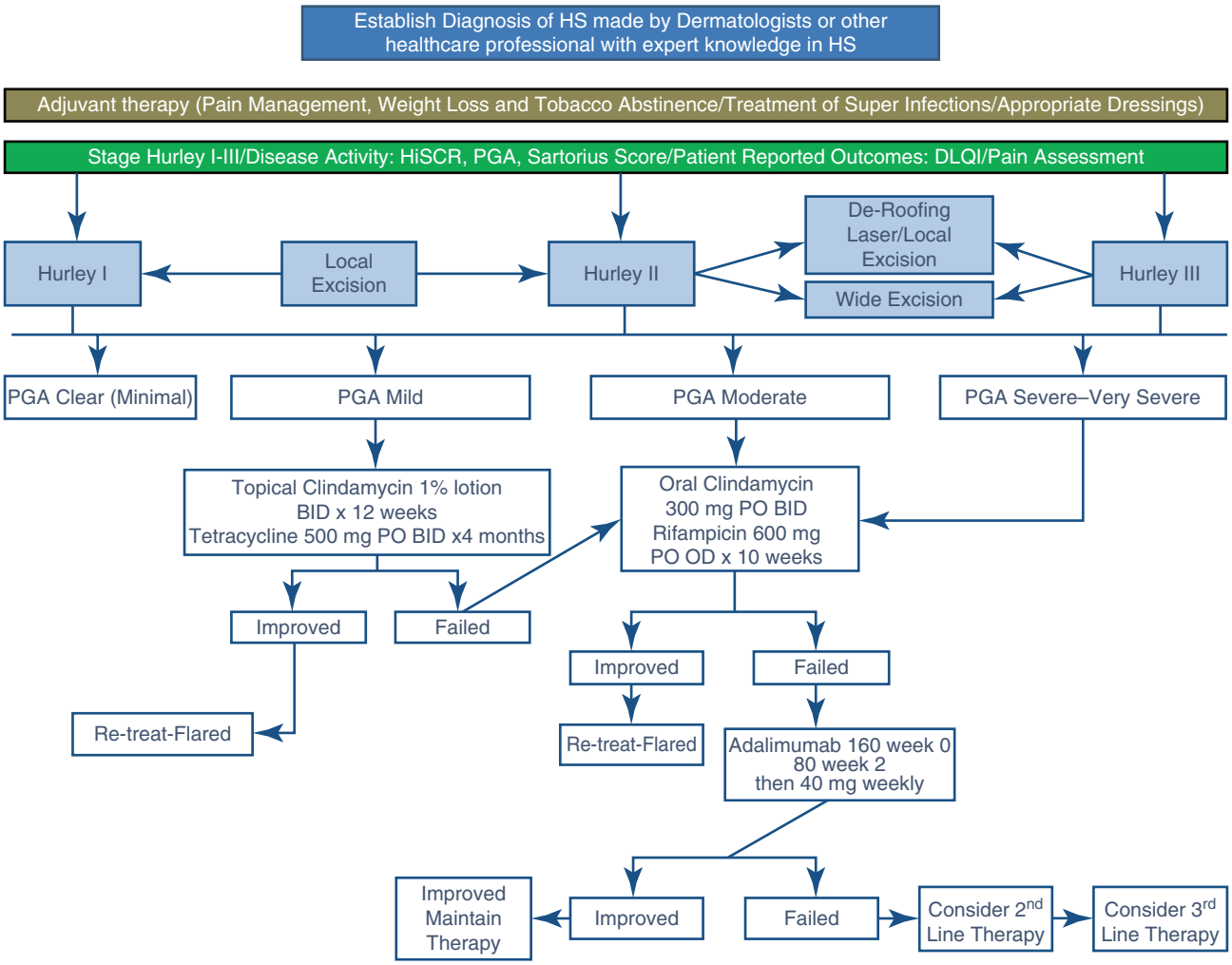

Fig. 36.2 Evidence-based HS treatment algorithm. Published in Gulliver W, Zouboulis CC, Prens E, Jemec GBE, and Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord. 2016;17:343–51

(160 mg at week 0, 80 mg at week 2, 40 mg weekly starting at week 4) is recommended. Surgical interventions personalized to the extent and severity of scarring or sinus tract formation, including options such as radical excision, deroofing, CO_2 laser, and Nd:YAG laser, are recommended to address those disease aspects not expected to respond to medical therapy.

The two therapeutic classes for which evidence is best are oral antibiotics and TNF monoclonal antibodies. The proportion of patients experiencing improvement with antimicrobial therapy are far higher than the proportion of patients with evidence from bacteriologic cultures of the presence of pathogenic bacteria. Because the reports on use of antimicrobial therapy are not placebo-controlled, it is possible that many of those patients who experienced improvement in their HS while receiving antimicrobial therapy may really be experiencing spontaneous waning in their disease severity that is unrelated to their antimicrobial therapy. Alternatively, the antimicrobial therapy may be exerting an anti-inflammatory effect or may be altering the proportions of commensal bacteria that are triggering inflammation in HS lesions, bacteria that are not easily cultured with routine bacteriological methods. Placebo-controlled trials of antimicrobial therapy in HS, preferably coupled with assessments of the cutaneous microbiomes before and after antimicrobial therapy, are needed to resolve this question. Antimicrobial therapy use in HS differs from use with true infectious dermatoses such as furunculosis because routine cultures are not warranted and should not be used to guide antimicrobial choice. The antibiotic therapy with the largest available efficacy and safety dataset in HS is combination clindamycin and rifampicin, which is typically administered for no more than 10 weeks because of the risk of inducing *C. difficile* colitis. Therapy with antibiotics in the tetracycline class or zinc gluconate is recommended to maintain

disease control after completion of the 10-week clindamycin-rifampicin treatment regimen [20]. TNF monoclonal antibody therapy, particularly adalimumab, has the largest evidence base supporting efficacy and safety for treatment of HS. In the absence of head-to-head trials, it is not possible to use the adalimumab and other biologic trial outcomes to infer comparative efficacy and safety: there are confounding differences in the baseline population, in the primary efficacy measure, and in the endpoint. Among therapies other than oral antibiotics and TNF monoclonal antibodies, retrospective series for zinc gluconate and acitretin report efficacy results that are higher than what would be expected to occur with placebo.

Limited surgical interventions may complement medical therapies to remove isolated, intermittently inflamed sinus tracts, with the surgery expected to be technically easier after inflammation is better controlled. The benefits and risks of larger-scale excision and of Nd:YAG or CO_2 laser surgery are uncertain because of variability in the recurrence risk and insufficient information about their postoperative morbidity.

Given the many limitations in the evidence base for HS treatments, and the real-world constraints dictated by payors about which treatments can be used, clinicians may be obliged to utilize a treatment algorithm without having confidence that all the choices in the algorithm are effective. It is reasonable to engage in empiric trials of unproven medical therapies, so long as the clinician and patient have the discipline to abandon therapies that are not resulting in clinically relevant improvement, or, if response is partial, to supplement with additional therapies expected to act through different mechanisms (e.g., oral antibiotics and TNF monoclonal antibodies). The absence of evidence of toxicity from combining these two classes in the PIONEER II trial further supports this treatment tactic. Two practical means of assessing if clinically relevant improvement is occurring are to collect at baseline and at each follow-up visit abscess plus inflammatory nodule counts and DLQI scores, neither of which are burdensome to collect. Clinically relevant improvement corresponds to at least 50% reduction in abscess plus inflammatory nodule count relative to baseline and/or a decrease from baseline in DLQI scores of at least 4. The severe quality of life impairment resulting from HS, and the risk of disease progression in patients whose inflammatory disease is inadequately controlled, should spur clinicians to change therapies for patients who are languishing on suboptimal therapy.

Case Report

A 45-year-old white female presents with a history of inflammatory lesions in the perianal area and medial thighs that have been present since she was a teenager. Some of the lesions drain fluid. Once to twice per month, she develops severely painful abscesses which persist for approximately a week. The abscesses are more likely to appear during the last week of her menses. Past treatment with doxycycline 100 mg twice daily helped reduce the pain and drainage but failed to resolve the lesions. She denies arthritis, abdominal pain, or diarrhea.

Past medical history: Noncontributory

Social History

- Drinks socially (a few glasses of wine per week)
- Nonsmoker
- Single
- Office worker

Previous therapies: Oral doxycycline

Physical Exam

- Axilla and inframammary folds are clear
- Three draining fistulas on bilateral medial buttock cheeks
- Hypertrophic bridging scars, bilateral medial thighs
- DLQI score of 11

Management

Doxycycline 100 mg po twice daily was continued, and twice daily clindamycin lotion to affected areas was prescribed. Because of the history of flaring during menses, the patient was started on spironolactone 25 mg po bid, which was ultimately increased to a dose of 100 mg po bid. These interventions further reduced her drainage, but because she complained of persistent flares of her abscesses, adalimumab was initiated. The QuantiFERON Gold assay test was negative and she had negative hepatitis B serologies. Adalimumab dosing was 160 mg at week 0, 80 mg at week 2, and then 40 mg weekly starting at week 4. The patient noted pain reduction within the first week of therapy and has remained on topical clindamycin, doxycycline, spironolactone, and adalimumab for several months.

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