

Treatment Stacking: Optimizing Therapeutic Regimens for Hidradenitis Suppurativa

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Hidradenitis suppurativa (HS) is a debilitating chronic condition that often is recalcitrant to first-line treatments, and mechanisms underlying its pathology remain unclear. Existing data suggest a multifactorial etiology with different pathophysiologic contributors, including genetic, hormonal, and immune dysregulation factors. At this time, only one medication (adalimumab) is US Food and Drug Administration approved for HS, but multiple medical and procedural therapies are available.¹ Herein, we discuss the concept of treatment stacking, or the combination of unique therapeutic modalities—an approach we believe is key to optimizing management of HS patients.

Stacking Treatments for HS

Unlike psoriasis, in which a single biologic agent may provide 100% clearance (psoriasis area and severity index 100 [PASI 100]) without adjuvant treatment,^{2,3} the field of HS currently lacks medications that are efficacious to that degree of success as monotherapy. In HS, the benchmark for a positive treatment outcome is Hidradenitis Suppurativa Clinical Response 50 (HiSCR50),⁴ a 50% reduction in inflammatory lesion count—a far less stringent marker for disease improvement. Thus, providers should design HS treatment regimens with a model of combining therapies and shift away from monotherapy. Targeting different pathophysiologic pathways by stacking multiple treatments may provide synergistic benefits for HS patients. Treatment stacking is a familiar concept in acne; for instance, patients who benefit tremendously from isotretinoin may still require

a hormone-modulating treatment (eg, spironolactone) to attain optimal results.

Adherence to a rigid treatment algorithm based on disease severity limits the potential to create comprehensive regimens that account for unique patient characteristics and clinical manifestations. When evaluating an HS patient, providers should systematically consider each pathophysiologic factor and target the ones that appear to be most involved in that particular patient. The North American HS guidelines illustrate this point by supporting use of several treatments across different Hurley stages, such as recommending hormonal treatment in patients with Hurley stages 1, 2, or 3.¹ Of note, treatment stacking also includes procedural therapies. Surgeons typically prefer a patient's disease management to be optimized prior to surgery, including reduced drainage and inflammation. In addition, even after surgery, patients often still require medical management to prevent continued disease worsening.

Treatment Pathways for HS

A multimodal approach with treatment stacking (Figure) can be useful to all HS patients, from those with the mildest to the most severe disease. Modifiable pathophysiologic factors and examples of their targeted treatments include (1) follicular occlusion (eg, oral retinoids), (2) metabolic dysfunction (eg, metformin), (3) hormones (eg, oral contraceptive pills, spironolactone, finasteride), (4) dysbiosis (eg, antibiotics such as clindamycin and rifampin combination therapy), (5) immune dysregulation

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doi:10.12788/cutis.0359



Targeted treatments for modifiable pathophysiologic arms of hidradenitis suppurativa (HS). Surgical and laser excisions (not shown) remove persistent inflamed and diseased tissue. Asterisk indicates mixed data in literature; should be considered in patients with severe acne. Dagger indicates exclusive usage in female HS patients. Double dagger indicates biologics including anti-tumor necrosis factor α , IL-1, IL-17, IL-12/23, and IL-23.

(eg, biologic agents), and (6) friction/irritation (eg, weight loss, clothing recommendations).

Combining treatments from different pathways enables potentiation of individual treatment efficacies. A female patient with only a few HS nodules that flare with menses may be well controlled with spironolactone as her only systemic agent; however, she still may benefit from use of an antiseptic wash, topical clindamycin, and lifestyle changes such as weight loss and reduction of mechanical irritation. A patient with severe recalcitrant HS could notably benefit from concomitant biologic, systemic antibiotic, and hormonal/metabolic treatments. If disease control is still inadequate, agents within the same class can be switched (eg, choosing a different biologic) or other disease-modifying agents such as colchicine also can be added. The goal is to create an effective treatment toolbox with therapies targeting different pathophysiologic arms

of HS and working together in synergy. Each tool can be refined by modifying dosing frequency and duration of use to strive for optimal response. At this time, the literature on HS combination therapy is sparse. A retrospective study of 31 patients reported promising combinations, including isotretinoin with spironolactone for mild disease, isotretinoin or doxycycline with adalimumab for moderate disease, and cyclosporine with adalimumab for severe disease.⁵ Larger prospective studies on clinical response to different combination regimens are warranted.

Optimizing Therapy for HS and Its Comorbidities

Additional considerations may further optimize treatment plans. Some therapies benefit all patients; for example, providers should counsel all HS patients on healthy weight management, optimized clothing choices,⁶ and friction reduction in the intertriginous folds. Providers

also may consider adding therapies with faster onset of efficacy as a bridge to long-term, slower-onset therapies. For instance, female HS patients with menstrual flares who are prescribed spironolactone also may benefit from a course of systemic antibiotics, which typically provides more prompt relief. Treatment regimens also can concomitantly treat HS and its comorbidities.⁷ For example, metformin serves a dual purpose in HS patients with diabetes mellitus, and adalimumab in patients with both HS and inflammatory bowel disease.

Final Thoughts

The last decade has seen tremendous growth in HS research⁸ coupled with a remarkable expansion in the therapeutic pipeline.⁹ However, currently no single therapy for HS can guarantee satisfactory disease remission or durability of remission. The contrast between clinical trials and real-world practice should be acknowledged; the former often is restrictive in design with monotherapy and allowance of very limited concomitant treatments, such as topical or oral antibiotics. This limits our ability to draw conclusions regarding the additive synergistic potential of different therapeutics in combination. In clinical practice, we are not restricted by monotherapy trial protocols. As we await new tools, treatment stacking allows for creating a framework to best utilize the tools that are available to us.

Although HS has continued to affect the lives of many patients, improved understanding of underlying pathophysiology and a well-placed sense of urgency from all stakeholders (ie, patients, clinicians, researchers, industry partners) has pushed this field forward. Until

our therapeutic armamentarium has expanded to include highly efficacious monotherapy options, providers should consider treatment stacking for every HS patient.

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