

ABOUT THE AUTHOR

Raed Alhusayen, MBBS, MSc, FRCPC

Dr. Alhusayen is Assistant Professor, Division of Dermatology, University of Toronto, Associate Scientist, Evaluative Clinical Sciences, Odette Cancer Research Program and Staff Physician, Division of Dermatology, Sunnybrook Health Sciences Centre. Dr. Alhusayen earned a Bachelor of Medicine, Bachelor of Surgery degree at the College of Medicine, King Saud University, Riyadh, Saudi Arabia. He then completed a residency in dermatology and a clinical fellowship in laser dermatology at the University of Ottawa. Dr. Alhusayen received a Master of Sciences degree in clinical epidemiology from the University of Toronto, where he also completed a clinical and research fellowship in advanced medical dermatology. As a dermatoeidemiologist, Dr. Alhusayen's areas of research interest include exploring prognostic indicators and measuring clinical outcomes, studying the risk of malignancy in patients with autoimmune skin disorders and assessing systemic comorbidities with skin diseases. Hidradenitis suppurativa is the main focus of Dr. Alhusayen's complex medical dermatology practice. He is the supervisor for clinical research in the advanced medical dermatology fellowship program. He is also the current president of the Canadian HS foundation.



MANAGEMENT OF HIDRADENITIS SUPPURATIVA IN SPECIAL PATIENT POPULATIONS

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease with an early age of onset. Medical therapies with anti-inflammatory properties are the mainstay of treatment. Tetracyclines, rifampicin plus clindamycin, and adalimumab are standard therapeutic approaches.¹ However, either due to lack of response or contraindications, many other medications are required in the management of the disease (Figures 1 and 2).^{2,3}

This is especially true as HS patients are at higher risk for a growing list of comorbidities including metabolic syndrome, inflammatory bowel disease, malignancy, depression, pyoderma gangrenosum, and psoriasis.⁴ Also, certain stages in life such as childhood and pregnancy can restrict treatment options. When appropriate, adjunct surgical interventions should be considered early to support the limited medical therapeutic options. In this article, we will discuss the management of HS in special patient populations (Table 1).

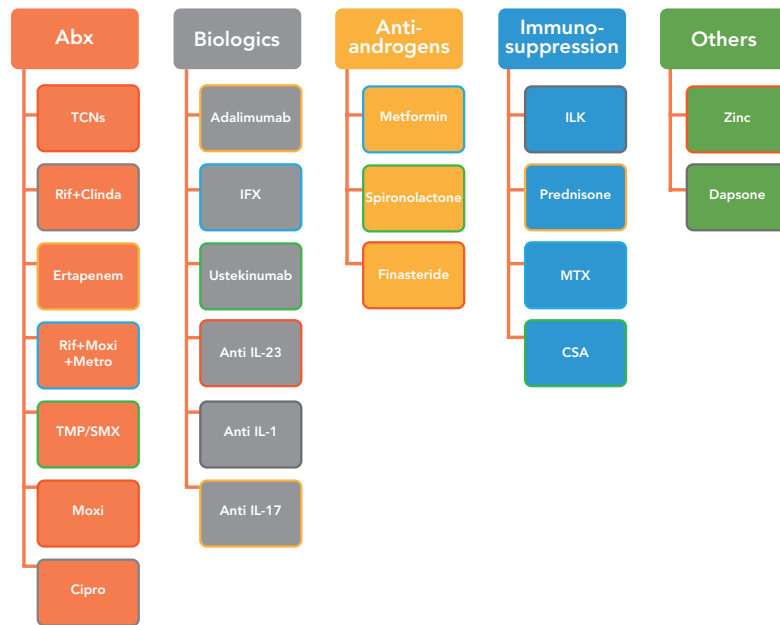


Figure 1. Treatment options for HS in special patient populations; table courtesy of Dr Raed Alhusayen

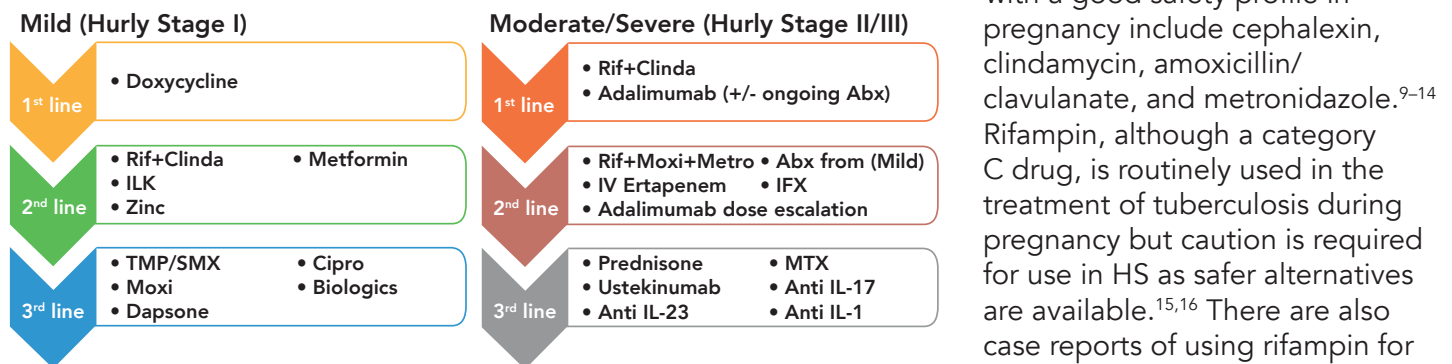


Figure 2. Stepwise approach for the management of HS; chart courtesy of Dr Raed Alhusayen

	POTENTIALLY GOOD OPTIONS	AVOID/CAUTION
PREGNANCY	ANTI-TNFS	TETRACYCLINES RIFAMPIN
INFLAMMATORY BOWEL DISEASE	METRONIDAZOLE CIPROFLOXACIN ANTI-TNFS ANTI IL-12/23	TETRACYCLINES CLINDAMYCIN ANTI IL-17
INFLAMMATORY ARTHROPATHIES	TETRACYCLINES ANTI-TNFS ANAKINRA SYSTEMIC STEROIDS	LEFLUNOMIDE
ADOLESCENCE	RIFAMPIN+CLINDAMYCIN CEPHALEXIN ANTIANDROGENS (METFORMIN, SPIRONOLACTONE, FINASTERIDE) ADALIMUMAB	TETRACYCLINES (UNDER THE AGE OF 8) SYSTEMIC STEROIDS
MALIGNANCY	TETRACYCLINES RIFAMPIN+CLINDAMYCIN SULFAMETHOXAZOLE/TRIMETHOPRIM ERTAPENEM	BIOLOGICS
PSORIASIS	ANTI-TNFS ANTI IL-12/23 ANTI IL-17 ANTI IL-23 CYCLOSPORINE	SYSTEMIC STEROIDS
PYODERMA GANGRENOSUM	DAPSONE MINOCYCLINE ANTI-TNFS ANTI IL-12/23 CYCLOSPORINE SYSTEMIC STEROIDS	

Table 1. Treatment options for HS in special patient populations; table courtesy of Dr Raed Alhusayen

Pregnancy

Only 20% of HS patients report symptom remission during pregnancy, with the majority (72%) reporting ongoing active disease and 8% experiencing worsening of symptoms.⁵ Many HS patients prefer not to take any medications during pregnancy. This is a reasonable option if someone has mild stable disease. In these cases, intralesional triamcinolone injections can be used for localized flares. In more severe disease, systemic therapy is almost always required. Tetracyclines should be avoided during pregnancy due to the risk of impaired bone growth and staining of the teeth.⁶⁻⁸ Antibiotics with a good safety profile in pregnancy include cephalexin, clindamycin, amoxicillin/clavulanate, and metronidazole.⁹⁻¹⁴ Rifampin, although a category C drug, is routinely used in the treatment of tuberculosis during pregnancy but caution is required for use in HS as safer alternatives are available.^{15,16} There are also case reports of using rifampin for the management of cholestatic pruritus in pregnancy.^{17,18} There is a growing body of evidence around the safety of anti-TNF biologics during pregnancy.¹⁹⁻²¹ The majority of these drugs cross the placenta in the third trimester and patients should be counselled about the implications to the newborn baby.^{21,22} The Centers for Disease Control and Prevention (CDC) recommends postponing live vaccines until the newborn is 6 months old if exposed to TNF-alpha inhibitors in the third trimester of pregnancy.²¹ The decision to either avoid, discontinue use in the third trimester, or continue anti-TNF therapy throughout pregnancy should be personalized to each patient's needs and preferences.

Anecdotally, the author has successfully used certolizumab,²³ an anti-TNF drug with a minimal placental transfer, to manage HS during pregnancy—although this use is off-label.

Inflammatory Bowel Disease

In a recent systematic review and meta-analysis which included 5 case-control studies, 2 cross-sectional studies, and 1 cohort study with a total of 93 601 unique participants, patients with hidradenitis suppurativa were found to have had a 2.12-fold increased odds for Crohn's disease (95% CI, 1.46-3.08) and a 1.51-fold increased odds for ulcerative colitis (95% CI, 1.25-1.82).²⁴

Patients with concurrent diagnoses pose an unique therapeutic challenge. Tetracyclines and clindamycin, commonly used in the management of HS, are usually avoided in this patient population. Tetracyclines have been linked with increased risk of developing inflammatory bowel disease (IBD), while clindamycin is a major risk factor for *C. difficile* infection which is a special concern in the IBD population.^{25,26} Good antibiotic options would be ciprofloxacin and metronidazole which are standard therapies for perianal IBD-related abscesses.²⁷ Furthermore, a randomized controlled trial (RCT) found adalimumab plus ciprofloxacin (71% response rate) superior to adalimumab monotherapy (47%) in treating perianal fistulating Crohn's disease ($p=0.047$) from baseline to week 12 with no difference in safety issues observed between the two groups.²⁸

Adalimumab is approved for HS and IBD. Both infliximab and ustekinumab are approved in IBD and were shown to be effective in the management of HS.²⁹⁻³⁴ Also, there is anecdotal evidence that guselkumab may be effective in

the management of HS and IBD.³⁵⁻³⁷ Low dose systemic steroids can be used as monotherapy or in combination with anti-TNF biologics.^{38,39} Methotrexate can also be added to anti-TNF biologics to prevent the formation of anti-drug antibodies.⁴⁰⁻⁴² Anti-IL-17 biologics should be avoided in this population due to the potential risk of IBD flare.⁴³⁻⁴⁵

Inflammatory arthropathies

In a retrospective case-control study, the unadjusted analysis showed that all comorbidities were diagnosed significantly more in the HS population as compared to the control population, including up to 52% of HS patients who have arthropathies ($P<0.01$).⁴⁶ There is a lack of awareness among clinicians about this association which could result in a delay in diagnosis and permanent joint damage. Seronegative spondyloarthritis is more common than rheumatoid arthritis in this group.⁴⁷⁻⁴⁹

Most HS treatments are safe to use in patients with inflammatory arthritis. Tetracyclines are effective in the management of mild rheumatoid arthritis making them a good first-line therapy in this patient population.⁵⁰ It is not clear if sulfasalazine, a standard treatment for inflammatory arthropathies, can be helpful in HS as it targets neutrophils which are major infiltrates in HS lesions.⁵¹⁻⁵³ A recent report described 2 patients who developed HS while on leflunomide for rheumatoid arthritis who improved a few weeks after discontinuation of the medication.⁵⁴

Adalimumab and infliximab, but not etanercept, are good options in this patient group.^{29,55-58} Also, in a small RCT ($N=20$), patients with Hurley stage II or III HS were randomized to received either anakinra, an anti-IL-1 β antibody,

or placebo. Results demonstrated that 78% of patients, in the anakinra arm, with moderate-to-severe HS achieved a Hidradenitis Suppurativa Clinical Response 50 (HiSCR 50) by week 12 ($P=0.04$).⁵⁹ The data on the efficacy of canakinumab, another anti-IL-1 β antibody, is not conclusive with conflicting findings from case reports.⁶⁰⁻⁶³ Systemic steroids may also help both conditions.^{38,64}

Pediatric HS

Approximately 7% of HS patients have disease onset by age 12.⁶⁵ Patients with early-onset are more likely to have a family history of the disease.⁶⁵⁻⁶⁷ As previously stated, tetracyclines are avoided in children under the age of 8 due to the impact on bone growth and teeth discoloration.^{6,68} Rifampin and clindamycin combination may be used in this population.^{66,67,69} Also, other antibiotics such as cephalexin and amoxicillin/clavulanic acid are alternative options. It has been suggested that hormonal abnormalities are more common in the pediatric HS population.^{66,67} Hence, antiandrogen therapies including metformin, spironolactone, and finasteride may be especially helpful.⁷⁰⁻⁷⁴

Adalimumab is approved for use in adolescents 12 years or older in weight-based dosing. Children weighing 30 kg to less than 60 kg receive 80 mg at week 0 then 40 mg every other week starting at week 1. Children weighing 60 kg or more receive adult dosing.⁷⁵ There is real-world data using biologics off-label in pediatric populations for other inflammatory conditions and these same biologic agents may be used in recalcitrant HS cases as well. These include infliximab and ustekinumab.^{76,77} Systemic steroids, although effective, should be avoided in the pediatric population due to the risk of

growth retardation.⁷⁸

Malignancy

In general, biologic therapies are not recommended to be used in patients with active cancer due to risks of immunosuppression and cancer progression.^{79,80} In patients with a past medical history of cancer, initiating biologic therapy depends on cancer type, time since remission, and HS severity.^{79,80} The decision should be made, preferably in consultation with the treating oncologist, after weighing benefits and risks. Commonly prescribed antibiotics for the management of HS can be used in cancer patients with minimal concern. While the use of antibiotics immediately before initiating checkpoint inhibitor immunotherapy was associated with significantly shorter survival (2 vs 26 months for prior antibiotic therapy vs no prior antibiotic therapy, respectively; hazard ratio [HR], 7.4; 95% CI, 4.2-12.9) in a study involving 196 patients with a median age of 68 years and with non-small cell lung cancer (n = 119), melanoma (n = 38), and other tumor types (n = 39), there were no negative implications when antibiotics were prescribed concurrently with these agents.⁸¹ In some cases, we can build on existing antibiotic therapy to achieve control of HS lesions. In a leukemia patient who underwent a stem-cell transplant and was placed on long-term sulfamethoxazole/trimethoprim prophylaxis, HS lesions developed after the dose of antibiotics was reduced to 3 times weekly. We were able to control the HS flare by restarting the daily dosing. In the most severe cases, a course of IV ertapenem is a reasonable choice.⁸² Also, low dose prednisone is an option in severe recalcitrant cases.³⁸

Psoriasis

Approximately 9% of HS patients have psoriasis.⁴⁷ For the most part, this creates an opportunity for HS patients to access medications approved for psoriasis that can also be effective in HS. Adalimumab is approved for both HS and psoriasis but the dosing in HS is double that for psoriasis.^{55,83} While etanercept wasn't found to be effective in HS, infliximab can be helpful especially at higher doses and/or frequency.^{56,84,85} Also, there are case series and phase II studies with positive results using ustekinumab, secukinumab, and guselkumab.^{33-35,86} For moderate HS, 53% of patients taking apremilast achieved HiSCR50 in a small randomized controlled study.⁸⁷ Cyclosporine is effective for both psoriasis and HS.^{2,3} Patients should be closely monitored as HS patients are at higher risk for metabolic syndrome which may manifest itself through hypertension and dyslipidemia.⁴ Antibiotics used to treat HS are generally safe to use in patients with psoriasis but they have no benefit in the latter condition. Similarly, systemic retinoids and methotrexate have a limited role in managing HS.⁸⁸ Finally, systemic steroids should be used with caution, if ever, due to the risk of psoriasis rebound upon medication withdrawal.⁸⁹

Pyoderma gangrenosum

The rate of pyoderma gangrenosum among HS patients is not clear but appears to be higher than the general population.^{90,91} Also, the 2 conditions could coexist as part of inflammatory syndromes such as PASH (PG, acne and suppurative hidradenitis) or PAPASH (pyogenic arthritis, acne, PG and suppurative hidradenitis).⁹²

Dapsone, an antineutrophilic agent, is a good option for both HS and PG.^{88,93-97} It can be used as monotherapy in mild cases or in combination for more severe cases. Similarly, there are several reports of successfully controlling PG using minocycline.⁹⁸⁻¹⁰¹ Systemic steroids and cyclosporine also are effective treatments.^{1,93,102-105} Among biologics, adalimumab, infliximab, and ustekinumab have data to support their use for both conditions.^{29,34,55,106-110} Finally, it is not clear if anakinra is effective in PG.^{111,112}

Conclusion

HS is associated with many comorbidities which provides challenges as well as opportunities in managing these patients. If possible, the preference is to choose treatment modalities that address all existing comorbidities. When that is not possible, treating physicians should ensure the selected treatments don't negatively impact any of these comorbidities.

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