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REVIEW ARTICLE

Hidradenitis Suppurativa in Children and Adolescents: An Update on Pharmacologic Treatment Options

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Abstract

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin condition that manifests as painful, deep-seated, inflamed nodules and abscesses in the axillary, groin, perianal, perineal, and inframammary regions. The associated pain, malodour, and disfigurement contribute to its profound negative impact on psychosocial spheres and overall quality of life in affected individuals. Although the symptoms of HS classically begin in the second or third decade of life, HS affects children and adolescents as well. Despite this, there are limited pediatric data on treatment, which are largely based on expert opinion, extrapolation of efficacy data in adults with HS, and safety information from medication use in other pediatric diseases. On this basis, there exist several pharmacological modalities in the treatment of children and adolescents with HS including topical therapies, systemic therapies, and biologics. The goals of this review article are to: (1) review the efficacy of different pharmacological treatment modalities in children and adolescents with HS, and (2) review the safety and monitoring considerations of the different treatment options in children and adolescents with HS.

Key Points

There is a large range of treatment options for pediatric hidradenitis suppurativa including topical, systemic, and biologic medications.

The treatment of pediatric patients with hidradenitis suppurativa is largely based on expert opinion, extrapolation of efficacy data from adult studies, and long-term pediatric safety data for drugs used in other pediatric inflammatory conditions.

Involvement of children and adolescent in hidradenitis suppurativa clinical trials with long-term follow up will improve knowledge of the true efficacy and safety in this cohort.

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1 Introduction

Hidradenitis suppurativa (HS), also known as acne inversa and/or Verneuil's disease, is a chronic, recurrent, inflammatory skin condition [1–4]. HS typically manifests in the intertriginous areas, such as the axillae, groin, perianal, perineal, and inframammary regions [1, 2]. The typical presentation is the development of painful, deep-seated, inflamed lesions such as nodules, sinus tracts, scarring, and abscesses in the second or third decade of life [1–3, 5]. The pathogenesis of HS is not fully understood, however, it appears to be multi-factorial involving follicular occlusion, genetic inheritance, bacterial colonization, and immunologic factors [6, 7]. Although not linked in a causative manner to HS, cigarette smoking, obesity, and mechanical trauma to the skin may be environmental risk/trigger factors in HS development [6, 7]. Patients living with HS experience a significant negative impact on their quality of life, even compared with several other dermatologic conditions [6]. The severity of HS is typically classified according to the Hurley clinical staging system, where Stage I indicates milder disease and Stage III indicates more widespread and severe disease [2–4, 8].

Another factor contributing to overall HS-related morbidity is the association with other comorbid dermatologic and nondermatologic medical conditions [1, 6, 7, 9]. HS may be seen in conjunction with disorders of follicular occlusion

including acne conglobata, dissecting cellulitis of the scalp, and pilonidal cysts, which make up the follicular occlusion tetrad [1, 2, 6, 10]. Notably, HS is commonly associated with severe and refractory acne vulgaris [2, 6]. HS is also associated with numerous systemic comorbidities including metabolic and cardiac, endocrine, gastrointestinal, rheumatologic, genetic, malignant, and psychiatric comorbidities (see Table 1) [4, 9, 11–13]. In a subset of patients, HS may be a component of an autoinflammatory syndrome, including but not limited to pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH); pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis (PAPASH); and psoriatic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis (PsAPASH).

Although HS is more common in adults, a significant number of patients diagnosed with HS are children and adolescents [14–17]. Pediatric patients are approximately twice as likely to report a positive family history of HS [14, 18–20]. Furthermore, those with early onset HS are more likely to develop lesions of similar severity at more body sites compared with adults [18, 19]. Compared with adults with HS, children with HS are more likely to have associated psychiatric comorbidity [11, 14]. Pediatric HS predominantly affects girls compared with boys, however the exact prevalence is not known [15, 16, 21]. In the pediatric population, HS is often misdiagnosed or associated with considerable diagnostic delay [22]. Furthermore, research regarding the management of pediatric HS is limited, with very few randomized clinical trials investigating the treatment options in this population. Therefore, the treatment of pediatric patients with HS is largely based on expert opinion, extrapolation of efficacy data from adult studies, and long-term pediatric safety data for drugs used in other pediatric inflammatory conditions. As such, further advocacy is needed for research specifically in children and adolescents with HS.

Table 1 Common HS comorbidities and associated conditions

Category	HS Comorbidity
Dermatologic	Severe acne vulgaris Acne conglobata Dissecting cellulitis of the scalp Pilonidal cysts Acanthosis nigricans
Metabolic and Cardiac	Obesity Metabolic syndrome Hypertriglyceridemia Diabetes mellitus Ischemic stroke Myocardial infarction
Endocrine	Polycystic ovarian syndrome Thyroid dysfunction
Gastrointestinal	Crohn's diseases Ulcerative colitis
Rheumatologic	Spondyloarthritis SLE
Malignancy	Lymphoma
Genetic	Trisomy 21
Psychiatric	Chronic pain Suicide Substance use disorder Decreased quality of life Increased risk of absenteeism from work/school

HS Hidradenitis suppurative, *SLE* Systemic lupus erythematosus

The goals of this review article are to: (1) review the different pharmacological treatment modalities available and the accompanying evidence for the treatment of children and adolescents living with HS, and (2) review the pharmacologic treatment considerations and monitoring of children and adolescents with HS. Although surgical and procedural interventions are a large component of HS treatment, they fall outside the scope of this review and are reviewed elsewhere [23].

We searched the MEDLINE medical database on 27 January 2023 and included all articles, regardless of date of publication. The key concepts for our search were "hidradenitis suppurativa," "pediatrics," and "treatment". In addition, we manually searched the reference list of other relevant articles on the treatment of pediatric HS. Titles, abstracts, and full text articles were screened by one author (N.C.). Inclusion criteria were the following: studies reporting on the pharmacologic treatment of children and adolescents (< 18 years old) with HS, studies published in the English language, and no restrictions were placed on study design. Sixty articles were deemed eligible for this narrative review (see Fig. 1). Where this search yielded no results for the treatment of pediatric HS, the search was expanded to include adults as needed. Furthermore, relevant guidelines for the treatment of adults with HS were reviewed for completeness.

2 General Considerations

For all patients living with HS, initial management includes nonpharmacological strategies, which based on the literature, are applicable to both adult and pediatric patients. The following safe and effective recommendations are important for all clinicians involved in the management of patients with HS, regardless of profession or discipline. Clinicians should educate patients and their parents about the natural history and course of HS [16, 24]. Goals of therapy should be clearly delineated, including to reduce or alleviate pain, minimize inflammation and scarring, and prevent disease progression [16]. Pediatric patients should be educated that HS is a chronic inflammatory condition that will need ongoing management, and

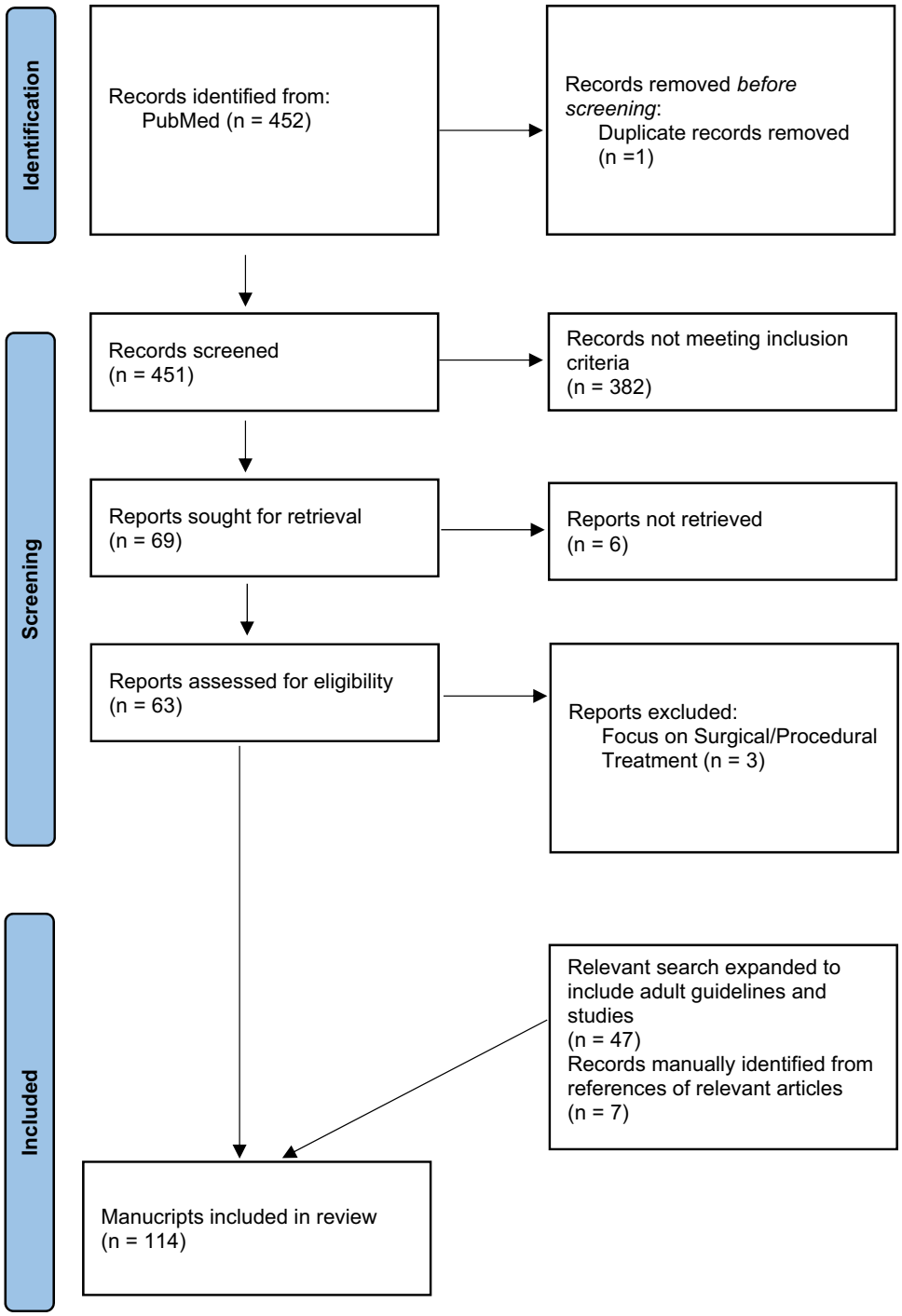

Fig. 1 PRISMA flow diagram of the selection and inclusion process of the studies for narrative review

that it is not contagious nor due to poor hygiene [16, 24]. This is especially important in children and adolescents as the psychological impact of the disease may impact their self-esteem and their social engagement during critical periods of development [16, 24, 25]. In addition to the dermatological exam, assessment of the following domains should be included in the initial consultation and monitoring: pain, itch, odour, functional limitations, and psychological impact [2, 24].

For all patients with HS, there are evidence-based non-pharmacological management strategies that have been shown to improve the severity and extent of disease involvement. In two pediatric cross-sectional studies in patients with HS, obesity was found to be a relevant factors associated with the severity and extent of HS involvement [26, 27]. Although directionality or causality could not be assessed in these studies, this finding is consistent with what is seen in adults with HS, where obesity is a well-defined risk factor

and has been successfully targeted as a potential treatment modality via dietary changes and weight loss strategies [28]. A retrospective chart review of 535 pediatric patients with HS suggests that there is a need for increased awareness, education, and counseling on weight management and nutrition, although further studies are needed to determine the efficacy of these interventions [29]. Furthermore, smoking has also been associated with HS in both adult and pediatric patients [13, 26]. Similar to obesity, there is no evidence that smoking cessation improves the extent and/or severity of HS; however, in pediatric patients with HS smoking has been identified as a risk factor for depression [30]. Smoking cessation is an important part of the management of these patients to prevent comorbid cardiovascular disease and mood disorders [13, 26, 27, 29, 30]. Similar to other inflammatory dermatologic conditions, wearing loose-fitting cotton clothing to reduce friction is recommended. Advice on wound and skin care management including guidance regarding draining lesions and wound dressings should be offered to all patients [2, 3].

Another important aspect of managing pediatric patients with HS is the assessment and management of the associated comorbidities of HS. Table 1 outlines the most common conditions that are associated with HS. Each follow-up visit should include screening for and assessment of these comorbidities, most notably obesity and psychiatric conditions [11, 12, 27].

3 Topical Therapies

Topical therapies are the most commonly prescribed medical treatments for pediatric HS and are first-line in Hurly Stage I HS, or milder, more localized diseases [3, 4, 15, 16, 31]. Topical therapies are generally considered safer due to the lessened chance of systemic effects, which is especially important in the pediatric population. The main topical therapies include clindamycin, resorcinol, antiseptics, and topical retinoids (see Table 2).

3.1 Clindamycin

Clindamycin is the most commonly used topical treatment in the management of pediatric HS [5, 15, 16, 26, 31]. Stemming from its well-studied use in adults, topical clindamycin has been the first-line treatment recommendation for Hurley Stage I and mild Stage II HS in children and adolescents, despite the lack of clinical trials in this population [5–7, 16, 32]. Topical clindamycin is considered to be safe in children as demonstrated by its long-term safety in the treatment of children with acne and other cutaneous infections [33–35]. If topical clindamycin is to be used as a long-term treatment plan, it should be combined with benzoyl peroxide to avoid the promotion of antibiotic-resistant bacteria.

3.2 Resorcinol

Resorcinol is a topical exfoliant and is the active ingredient of various over-the-counter acne products. It is also one of the most commonly used topical options in the treatment of pediatric HS when used in concentrations of 15% [17]. Resorcinol has not been evaluated in randomized clinical trials; however, in open-label and cross-sectional observational studies including 12 and 32 adults respectively, it was effective and safe in the treatment of mild-moderate HS [36, 37]. In one pediatric cross-sectional study, it was found that resorcinol had a response rate of up to 63%, however, this should be interpreted with caution as 7 of the 27 (26%) using resorcinol reported not knowing if they responded [17]. Historically, resorcinol was considered to be dangerous for children due to reports of poisonings, however with safe handling and with avoiding oral consumption, these risks can be mitigated [5]. Adverse effects are generally limited to local desquamation.

3.3 Topical Antiseptics

The recommendations for the use of topical antiseptics, such as benzoyl peroxide, chlorhexidine, or triclosan, are conflicting. While there is no evidence demonstrating its effectiveness in children or adults with HS, its use is generally recommended by dermatologists and guidelines in the treatment of HS [3–5, 15, 16, 31, 38]. Topical antiseptics' use in HS is primarily to reduce the bacterial load in and around any lesions. In addition, their use may reduce the risk of developing bacterial resistance to certain antibiotics [39]. Topical antiseptics are likely to be ineffective as monotherapy but are a reasonable recommendation as adjuvant therapy in HS of all severities [4, 14, 16, 31, 38, 40].

3.4 Topical Retinoids

The use of topical retinoids in HS is much less described in the literature compared with the other topical options. No formal studies have been conducted in adults or children. Based on the European HS guidelines in adults, expert opinion suggests that the use of adapalene may occasionally be beneficial [3]. Based on its use in the treatment of acne, it may have a place in pediatric HS patients with a heavy comedone burden or concomitant acne.

Table 2 Summary of Topical Therapies in the Treatment of Pediatric HS

Treatment	Efficacy	Safety	Monitoring	Level of evidence in children and adolescents
Topical Clindamycin 1% BID	Most used medical treatment for children, adolescents, and adults with HS Effective for localized disease of mild-to-moderate severity	Wide historical use in pediatric acne and superficial infections indicates it is very safe Negligible systemic absorption expected	Signs of local skin reaction	Case series/reports [5, 15, 16, 26, 31]
Resorcinol 15% BID	Very commonly used topical treatment in children and adolescents Effective for localized disease of mild-to-moderate severity	Generally considered safe to use in children and adolescents May cause contact dermatitis and/or reversible hyperpigmentation. Oral ingestion of resorcinol should be avoided	Signs of local skin reaction	Case series/reports [17]
Antiseptics (Benzoyl peroxide, chlorhexidine, triclosan) Daily	No evidence to support treatment in adults of children. Recommended by expert opinion on all patients with HS as an adjuvant therapy. May reduce antimicrobial resistance to certain antibiotics	Very safe	Signs of local skin reaction	Expert opinion and extrapolation from adult guidelines [5, 15, 16, 31]
Topical Retinoids Daily	No evidence to support treatment in adults or children May be useful in the treatment of HS with concomitant acne based on adult guidelines	Generally considered safe to use in children and adolescents based on its use in other indications May cause burning, itching, exfoliation of the skin, and skin irritation	Signs of local skin reaction	Expert opinion and extrapolation from adult guidelines [3]

BID twice daily, *HS* Hidradenitis suppurativa

4 Systemic Therapies

Systemic therapies are the mainstay of treatment for moderate to severe HS, or when topical therapy is ineffective [1, 3, 4]. The armamentarium of systemic therapies for HS includes systemic antibiotics, corticosteroids, immunomodulators, hormonal therapies, retinoids, metformin (Table 3), and biologic therapies (Table 4). One of the most important factors that clinicians and parents consider in the systemic treatment of pediatric conditions is the safety of the treatment in children. What makes clinical decision-making in pediatric patients with HS even more challenging is the lack of specific safety data in this population [14–16, 24, 26, 41]. Clinicians must extrapolate safety data from either adult studies in the treatment of HS, or pediatric studies in the treatment of other conditions. Parents of children with HS may be hesitant to use systemic therapies, as they may worry about the safety of the medication, so proper education about the benefits and risks of the various options is crucial for parent and patient buy-in.

4.1 Zinc

In a pilot study conducted in 22 adults, zinc gluconate supplementation had a 100% response rate [42]. In a cross-sectional study in pediatric patients with HS, zinc supplementation was one of the most frequently used treatment regimens [26]. It should be noted that patients using zinc supplementation for over 3 months should be counseled on the risk of hypocupremia, and offered copper supplementation to prevent secondary copper deficiency, with a recommended ratio of zinc:copper of 9:1 [43].

4.2 Oral Antibiotics

4.2.1 Rifampin + Clindamycin

The combination of rifampin and clindamycin is the most well-studied antibiotic combination in treating adults with HS [4]. A systematic review of retrospective and prospective series demonstrated the response rate ranges from 71 to 93% [44]. Furthermore, in a prospective pilot study in children and adolescents with HS, 20 out of 20 (100%) participants responded to the treatment, and most children had a reduction in the severity of HS by ≥ 50% [45]. This is one of the few prospective studies investigating treatment options specifically in children with HS. In both adults and children, the trials investigated a 10-week course of combination therapy [4, 45, 46]. The combination of rifampin and clindamycin may cause antibiotic-associated diarrhea, *Clostridioides difficile*-associated diarrhea, or, rarely, hepatotoxicity. The combination of rifampin and clindamycin is generally considered to be a very effective and safe treatment option in children with HS and should be considered a first-line oral treatment [5, 14, 16, 17, 45]. It should be noted that an increasing number of countries are discouraging the use of rifampin due to the development of multi-drug resistant tuberculosis (TB), and the use of clindamycin alone has been studied as an alternative in adults with HS [47–49].

4.2.2 Tetracyclines

The tetracycline antibiotics (tetracycline, doxycycline, and minocycline) are considered safe and effective and are used widely in adults for their antibacterial and anti-inflammatory properties [1, 3, 4, 6, 40]. There are no randomized, placebo-controlled clinical trials investigating the efficacy and safety of tetracyclines in adults or children with HS, with data gleaned largely from case reports and observational studies [6]. A double-blind head-to-head trial in 46 adults with mild-to-moderate HS found that there is no significant difference between topical clindamycin and tetracyclines at 16 weeks [50]. It is important to note that the patients' overall evaluation of disease activity in the tetracycline group trended to be better than the clindamycin group, while the physician's overall evaluation of disease activity in the clindamycin group trended to be better than the tetracycline group [50]. A cross-sectional study reported that 30 out of 55 (56.3%) adolescents who underwent treatment with a tetracycline antibiotic responded to treatment [17]. The usual treatment duration is for at least 12 weeks, or longer as maintenance when indicated [3, 4, 50]. The most commonly cited tetracycline used in the literature is doxycycline, however this does not seem to be evidence-based, and alternative tetracyclines could be used [16, 51, 52]. Although tetracyclines are a safe and effective option in adults, their safety in children has been the subject of debate. Tetracycline antibiotics are believed to cause dental staining and enamel hypoplasia in children under the age of 10 years, however, several studies have failed to show this side effect [53, 54]. Tetracyclines have been associated with esophagitis, photosensitivity, and skin hyperpigmentation. A rare adverse effect of tetracycline antibiotics includes pseudomotor cerebri, and this risk can be increased with the use of oral retinoids, therefore their concurrent use is contraindicated. There are numerous case reports about the use of tetracyclines in children ≥ 10 years old, however, the safety in children younger than 10 is not well elucidated [15–17, 20, 31].

4.2.3 Dapsone

Dapsone is another antibiotic option in the treatment of HS in adults. It is believed that dapsone's mechanism of action stems from its inhibition of neutrophil chemotaxis, rather

Table 3 Summary of systemic therapies in the treatment of pediatric HS

Treatment	Efficacy	Safety	Monitoring	Level of evidence in children and adolescents
Antibiotics				
Rifampin 300 mg + Clindamycin 300 mg BID for 10 weeks	Very effective option and most well studied antibiotic combination in the treatment of pediatric HS	Generally considered safe to use in children and adolescents based on one small prospective open-label pilot study and its use in other indications. Notable side effects include diarrhea and gastrointestinal upset	Baseline: LFT, serum creatinine, CBC. Ongoing: monitor for diarrhea and signs of liver injury	Pilot, prospective, noncomparative study with 20 patients aged ≤ 16 years [45]
Tetracyclines (Tetracycline 500 mg BID, Doxycycline 100 mg BID, Minocycline 100 mg BID) for ≥ 12 weeks	At least as effective as topical clindamycin Can be an effective option in adolescents.	Not recommended for use under 9 years old due to dental side effects Has been used safely in adolescents in other indications	Ongoing: CBC, renal and liver function tests periodically with prolonged therapy	Case series/reports and extrapolation from adults [15, 16, 31]
Dapsone 25–200mg daily for ≥ 12 weeks	No evidence to support use in children or adolescents May be an effective second-line option in mild-to-moderate HS	Generally considered safe to use in children and adolescents based on its use in other indications. Notable side effects include headache, fatigue, blood count abnormalities, and mood changes	Baseline: G6PD levels, CBC, LFTs Ongoing: CBC monthly, and patients should be monitored regularly for signs of jaundice, hemolysis, and blood dyscrasias	Case series/reports and extrapolation from adults [15]
Ertapenem 1 g daily for 6 weeks	No evidence to support use in children or adolescents May be effective rescue therapy in patients with severe HS	Generally considered safe to use in children and adolescents based on its use in other indications. Notable side effects include anaphylaxis, seizures, and relapse of symptoms after discontinuation	Ongoing: Periodic renal, hepatic, hematopoietic, and neurological assessment during prolonged therapy	Expert opinion and extrapolation from adults [4, 60, 61]
Immunomodulators				
Oral Corticosteroids—Prednisone daily	Generally effective at treating acute flares or refractory disease in the short-term	Not suitable for long-term use due to well-known risk of side effects May cause rebound inflammation after discontinuation of treatment	Ongoing: Blood pressure, weight, serum glucose, electrolytes, creatinine kinase, growth velocity, signs of infection, bone mineral density, signs of HPA axis suppression, and periodic CBC with prolonged treatment	Expert opinion and extrapolation from adults [3, 4, 6]
Intralesional Corticosteroids—Triamcinolone 10–40 mg/mL x 0.2–2 mL	May be effective at reducing the inflammation or nodules and other lesions, based on adult data, however the evidence is conflicting.	Low risk of systemic side effects with intralesional administration May cause local effects such as atrophy, pigmentary changes, and telangiectasia. Contraindicated if bacterial infection is present	Baseline: Signs of local infection Ongoing: Signs of infection and skin changes	Expert opinion and extrapolation from adults [3, 4, 67]

Table 3 (continued)

Treatment	Efficacy	Safety	Monitoring	Level of evidence in children and adolescents
Cyclosporine 2–5 mg/kg/day	May be beneficial in recalcitrant cases of HS. No evidence for use in children and adolescents	Generally considered safe in children based on its use in other indications. Should consider other options based on the risks of adverse effects. Counseling about the potential side effects should be offered to patients and their parents	Baseline: Blood pressure, creatinine, BUN, CBC, lipid profile, magnesium, potassium and uric acid Ongoing: Blood pressure, CBC, creatinine, lipid profile every other week for the first 3 months, then monthly thereafter	Expert opinion and extrapolation from adults [3, 4, 70]
Hormonal therapies				
Spironolactone 25–100mg divided once to twice daily or Anti-Androgenic Combined Oral Contraceptives	No evidence to support its use in children or adolescents. May be an effective option for girls with concomitant polycystic ovarian syndrome	Both are considered safe in adolescents based on well-studied use in acne	Spironolactone: Blood pressure, serum electrolytes, uric acid, kidney function, volume status periodically while on prolonged therapy COCs: Pregnancy status, personal or family history of thrombotic disorders, blood pressure, weight	Expert opinion and extrapolation from adults [74, 122]
Finasteride 1.25–5 mg daily	Case series have shown that it may be an effective treatment option in female children and adolescents	No side effects were reported in the case series, however long-term data are lacking, so judicious use is recommended	Signs of abnormal pubertal development	Case series/reports [77, 78]
Anti-Hyperglycemics				
Metformin 500 mg–2000 mg once to twice daily	No evidence to support its use in children or adolescents. May be an effective option for obese children or girls with polycystic ovarian syndrome	Considered to be safe in children and adolescents based on its use in pediatric diabetes	Baseline: Glucose, HbA1c, renal function Ongoing: Renal function, HbA1c	Expert opinion and extrapolation from adults [71, 81]
Retinoids				
Isotretinoin 0.5 mg–1 mg/kg/day	Efficacy in adults is questionable. May be more effective in mild-moderate disease, female, young patients who weigh less with a history of acne. Some case reports stating it may be effective in children	Significant safety profile including dermatologic, rheumatologic, and psychiatric adverse effects. Should only be prescribed by physicians who are familiar with its safety profile	Baseline: CBC with differential, ESR, glucose, signs and symptoms of psychiatric conditions, pregnancy status, lipid profile, liver function tests Ongoing: CBC with differential, signs and symptoms of psychiatric effects, severe skin reactions, changes in vision, signs and symptoms of pseudomotor cerebri, pregnancy status, lipid profile, liver function tests	Case series/reports [16, 77, 89]

Table 3 (continued)

Treatment	Efficacy	Safety	Monitoring	Level of evidence in children and adolescents
Acitretin 10–50 mg daily	Likely to be more effective than isotretinoin based on adult data. No trials investigating its efficacy in this population	Significant safety profile including dermatologic, rheumatologic, and psychiatric adverse effects. Should only be prescribed by physicians who are familiar with its safety profile	Baseline: CBC with differential, ESR, glucose, pregnancy status, lipid profile, liver function tests Ongoing: CBC with differential, severe skin reactions, pregnancy status, lipid profile, liver function tests	Expert opinion and extrapolation from adults [91, 92]

BID twice daily, *BUN* blood urea nitrogen, *CBC* complete blood count, *COC* combined oral contraceptive, *G6PD* glucose-6-phosphate dehydrogenase, *ESR* erythrocyte sedimentation rate, *HbA1c* hemoglobin A1c, *HPA* hypothalamic-pituitary-adrenal, *HS* Hidradenitis suppurative, *kg* kilogram, *mg* milligram, *mL* millilitre, *LFT* liver function test

than its antimicrobial properties [3, 4, 6]. Based on one retrospective review of 24 adults with HS, the response rate was 38%, however, none of the participants with severe HS (Hurley Stage III) responded to dapsone [55]. Furthermore, another retrospective review of 122 adults found that tolerability was a significant barrier to continuing treatment [56]. For this reason, guidelines in adults recommend dapsone as a second or third-line option, reserved for patients with mild-to-moderate disease [3, 4]. Treatment is recommended for at least 3 months, or longer as maintenance therapy if indicated. Dapsone has been prescribed in pediatric patients with HS, however, its use is much less described in the literature [15]. Dapsone is used in children for various dermatological and infectious reasons and is considered to be safe [57–59]. Prior to the initiation of dapsone, clinicians should perform baseline blood work including glucose-6-phosphate dehydrogenase (G6PD) levels, complete blood count (CBC), and liver function tests (LFTs). While on therapy, a CBC should be obtained monthly, and patients should be monitored regularly for signs of jaundice, hemolysis, and blood dyscrasias. Furthermore, therapy with dapsone may artificially lower hemoglobin A1c by reducing erythrocyte survival time through hemolysis, so patients with comorbid diabetes should be monitored via other markers.

4.2.4 Ertapenem

For patients with severe infections secondary to HS, ertapenem is an effective antibiotic option. Ertapenem is a broad-spectrum, intravenous, beta-lactam antibiotic that was very effective as rescue therapy in a retrospective study performed in 30 adults with HS [60]. After 6 weeks of treatment, 59% of HS areas affected by Hurley stage I or II achieved clinical remission, and most patients with Hurley stage III had major improvement in quality of life [4, 60]. The duration of therapy with ertapenem ranged from 6–9 weeks [60, 61]. The use of ertapenem is limited due to the requirement of IV access during the course of treatment. Although ertapenem is generally quite safe, its use has been rarely associated with an increased risk of seizures. There are no trials using ertapenem in pediatric patients with HS, however, it has been used safely in children for other severe infections [62–65].

4.2.5 Other Antibiotics

Other classes of antibiotics including fluoroquinolones, erythromycin, metronidazole, sulfamethoxazole, cephalosporins, and carbapenems have been anecdotally reported to have benefits in some adults with HS, however, there is a lack of published evidence [3, 4]. The use of these antibiotics should be guided by the presence of active cutaneous infection, colonization patterns, and patient preference.

Table 4 Summary of biologic therapies in the treatment of pediatric HS

Treatment	Efficacy	Safety	Monitoring	Level of Evidence in Children and Adolescents
TNF-alpha inhibitor: Adalimumab Initial: 160 mg, followed by 80 mg 2 weeks later Maintenance: 40 mg every week beginning on day 29	PIONEER-1 and POINEER-2 landmark trials demonstrate efficacy in the treatment of adults with HS. Currently only biologic approved for adolescents. No trials to support its use in children and adolescents	Increased risk of infection, injection site reaction, antibody development	Baseline: CBC with differential, complete metabolic panel, tuberculosis screening, hepatitis B/C screening, HIV screening Ongoing: Signs/symptoms of infection, hypersensitivity reaction, new auto-immune disorder, and malignancy	Pharmacokinetic and pharmacodynamic modelling [102] Case series/reports [90, 104, 105]
TNF-alpha inhibitor: Infliximab 5 mg/kg body weight on day 0, 2, 6 and then every 8 weeks	Several clinical trials demonstrate efficacy in the treatment of adults with HS. No trials to support its use in children and adolescents.	Increased risk of infection, injection site reaction, antibody development		Case series/reports [104, 105]
IL-17a inhibitor: Secukinumab 300 mg every week for 4 weeks, then every 2 weeks	SUNSHINE and SUNRISE trials efficacy in the treatment of adults with HS. No trials to support its use in children and adolescents	Increased risk of infection, injection site reaction, exacerbation of inflammatory bowel disease	Baseline: CBC with differential, complete metabolic panel, tuberculosis screening, hepatitis B/C screening, HIV screening, signs or symptoms of inflammatory bowel disease Ongoing: Signs/symptoms of infection, hypersensitivity reaction, inflammatory bowel disease, and malignancy	Extrapolation from adults [108]
IL-12/23 inhibitor: Ustekinumab 90 mg every 4 weeks for 8 weeks, then every 8 weeks	Several clinical trials demonstrate efficacy in the treatment of adults with HS. No trials to support its use in children and adolescents	Increased risk of infection, injection site reaction, antibody development	Baseline: CBC with differential, complete metabolic panel, tuberculosis screening, hepatitis B/C screening, HIV screening Ongoing: Signs/symptoms of infection, hypersensitivity reaction, squamous cell skin carcinoma, and malignancy	Case series/reports [105]

CBC complete blood count, *HIV* human immunodeficiency virus, *HS* Hidradenitis suppurative, *IL* interleukin, *mg* milligram, *TNF* tumor necrosis factor

4.3 Immunomodulators

4.3.1 Prednisone

Like in the treatment of most inflammatory conditions, systemic corticosteroids are not recommended in the treatment of HS for long-term use due to the many possible side effects [3, 4]. Furthermore, there are important safety considerations regarding the use of systemic steroids in the pediatric population including potential impact on bone mineral density, growth velocity, steroid-induced hyperglycemia, weight gain, and mood disturbances. They can be effective at reducing inflammation caused by acute flares, however, the effects of corticosteroids are short-lived and often lead to rebound inflammation [3–6]. There is little to no consensus or case reports of its use in children and adolescents.

4.3.2 Intralesional Corticosteroids

The benefit of intralesional corticosteroids is not well understood. In adults with HS, intralesional injection of triamcinolone (10–40 mg/mL × 0.2–2.0 mL) are thought to reduce erythema, edema, suppuration, and size of lesions with an onset of 24–72 h [3, 4, 6, 66]. More recently, a randomized controlled trial of 32 participants investigated the effectiveness of two concentrations of intralesional triamcinolone versus normal saline and showed no statistical or clinical difference [67]. This study design allowed for individual subjects to have multiple lesions randomized to distinct treatment arms, so that the total number of lesions was 55, despite only 32 participants enrolling in the trial [67]. In addition, others have commented on the dose of intralesional triamcinolone as another limitation of this study, potentially explaining the lack of efficacy [68]. Doses in other studies that have shown success range from 3 to 20 mg per nodule, whereas this study used 4 mg as their active control group [67–69]. For these reasons, further research is needed to establish the efficacy and dosing of intralesional corticosteroids. Although intralesional injections have been used successfully in children, there is no prospective evidence to support their use in children or adolescents with HS [21]. In one retrospective review, all nine patients who had received intralesional corticosteroids had responded to treatment [31]. There is little systemic absorption with intralesional injections, and so the risk of systemic side effects is greatly reduced compared with oral corticosteroids [3]. Intralesional corticosteroids should not be used in patients with evidence of local infection.

4.3.3 Cyclosporine

Given its inflammatory nature, other immunosuppressive agents, such as cyclosporine, have been used in the treatment of HS [1]. In one retrospective case series of 18 adults with HS, 50% of patients reported some benefit while on cyclosporine, particularly those with recalcitrant cases of HS [70]. The treatment duration of these patients ranged from 0.5 to 14 months [70]. Guidelines on HS generally state that cyclosporine should be considered a third-line treatment where other therapies have not been effective due to the lack of compelling and well-designed evidence to support its use in the treatment of adults with HS [3, 4, 66]. There is no evidence to support its use in children and adolescents. There are numerous side effects associated with cyclosporine, including diabetes, gingival overgrowth, hepatotoxicity, hyperkalemia, hypertension, increased risk of infections, increased risk of malignancy, nephrotoxicity, and neurotoxicity.

4.4 Hormonal Therapies

4.4.1 Spironolactone and Anti-Androgenic Combined Oral Contraceptives (COCs)

Historically, it was proposed that one of the pathophysiological mechanisms that causes follicular occlusion of the apopilosebaceous gland in HS was mediated by androgenic hormones [6]. Later studies and systematic reviews showed that this is partially true, particularly in a subgroup of female patients, where anti-androgenic therapies can be useful and helpful [71, 72]. Spironolactone has been shown to also be effective in combination with other classes such as retinoids and biologics [73]. Although still a topic of debate among experts, however, hormonal therapies are still considered an acceptable option in female patients, particularly if they have concomitant polycystic ovarian syndrome [3, 4, 40, 71]. Some examples of anti-androgenic combined oral contraceptives include those containing cyproterone or drospirenone. The most recent guidelines in adults suggest that hormonal therapies can be used as monotherapy in women for mild-to-moderate HS or in combination with other systemic therapies for more severe disease [3, 4]. The evidence to support the use of spironolactone or combined oral contraceptives in children is limited. One cross-sectional analysis reported that the use of spironolactone in adolescents with HS has been increasing by 2- to 3-fold from 2014 to 2018 and that more studies investigating the safety in this population are needed, particularly the effects of anti-androgens on development during puberty [74].

4.4.2 Finasteride

Finasteride is a more well-studied hormonal treatment option in the treatment of pediatric HS. In adults, several case reports have documented clinical improvements in HS with finasteride [75, 76]. Two case series investigating

the use of finasteride have been published in three and five children with HS and have both shown it to be a very effective option as monotherapy early on in the disease or as an adjunct option if topical or oral antibiotics have not yielded adequate improvement in both boys and girls [77, 78]. These patients have received treatment with finasteride ranging from 1 year to up to 6 years duration [77, 78]. Both of these case series did not show any safety concerns, however, the authors recommend judicious use of finasteride due to the lack of long-term safety data in children [77, 78]. In adults, finasteride is notably associated with decreased libido in both men and women, as well as impotence and ejaculatory disorder in men [79, 80].

4.5 Metformin

Although the mechanism is not well understood, HS is associated with insulin resistance, even when adjusting for age, sex, and body mass index [40, 81, 82]. Metformin has the benefit of not only increasing the effect of insulin and increasing glucose utilization by muscle and fat cells but also has an anti-inflammatory effect on several cell types [40, 71]. As such, several studies have investigated the use of metformin in the treatment of adults with HS [71]. In one prospective study, 24 weeks of metformin use was associated with significant improvement in the severity of HS in 16 of 25 patients (64%), where most of these patients were females with features of polycystic ovarian syndrome [81]. In adults, metformin may be an effective treatment as monotherapy in milder cases, or as an adjunct therapy in more severe cases that can help with both the HS itself, as well as treating potential comorbidities. There is no evidence to support the use of metformin in children or adolescents, however, based on its use in pediatric type 2 diabetes, metformin appears to be safe in children [83–85]. As with most patients, the dose of metformin should be titrated slowly to limit intolerable GI side effects, such as diarrhea.

4.6 Retinoids

4.6.1 Isotretinoin

Both the North American and European guidelines for the management of adults with HS report that the therapeutic effect of isotretinoin is questionable [3, 4]. Retinoids have been used historically, likely because the pathogenesis of HS was presumed to be similar to acne vulgaris, however retrospective studies fail to show consistent efficacy in the treatment of HS [3, 38, 66, 86, 87]. One retrospective chart review in 2017 of 25 adults has shown that isotretinoin may be effective in patients with mild and moderate disease and patients who are female, younger, weigh less, and have a personal history of acne [88]. The response rate was 68% and the patients in this study were treated with isotretinoin for a mean dose and duration of 0.45 mg/kg/day for 6.8 months [88]. There are some case reports of isotretinoin being used in children with moderate success of HS, with most of the children also having concomitant acne [77, 89]. Conversely, others have concluded that because isotretinoin has questionable efficacy in adults, it should not be trialled in children [21, 90]. Isotretinoin has a notable list of side effects that should be discussed with patients including, but not limited to, dry lips and skin, decreased bone mineral density, increased liver enzymes, hypertriglyceridemia, pancreatitis, myalgia, arthralgia, eye irritation, and psychiatric effects. Generally, the safety profile of isotretinoin makes it a less desirable therapy, and it should only be prescribed by physicians who are familiar with its side effects and can implement a monitoring plan accordingly. Isotretinoin may be recommended as a third- or fourth-line option for the treatment of HS in children or can be used in the treatment of concomitant acne.

4.6.2 Acitretin

Acitretin appears to be superior to isotretinoin in the treatment of adults with HS, however robust head-to-head trials are lacking [3, 4]. In one retrospective study in 12 patients, and in one prospective study in 17 patients, acitretin was shown to be an effective option for HS with response rates ranging from 90 to 100% in those who completed the study [91, 92]. It is important to note that in the prospective trial, only nine patients finished the whole 9 months of the acitretin monotherapy trial [92]. The safety profile is similar to isotretinoin and is a significant consideration when choosing therapy. Similar to isotretinoin, there are few case reports showing its efficacy [93]. Although it may be a more suitable option compared with isotretinoin in the treatment of children with HS based on its efficacy, its significant safety profile places it as a second or third-line option, again favoured in those with concomitant acne. Fertile pediatric patients of child-bearing potential on acitretin should be counseled about the teratogenic risk during treatment and for at least 3 years after taking acitretin owing to the risk of esterification and deposition of acitretin in adipose tissue [94–96].

5 Biologic Therapies

Historically, clinicians had limited success with the pharmacologic armamentarium in the treatment of patients with severe HS. With the development of biologic therapies, mainly monoclonal antibodies targeting various inflammatory cytokines, there was hope that immunomodulation would be a more specific treatment for these patients [3, 4, 97]. Biologics have had success in many dermatologic

conditions such as psoriasis and eczema, however, due to the cost and more intensive monitoring, they are typically reserved for more severe disease. With more studies being carried out in the pediatric population, clinicians have been eager to learn about the role of biologics in the treatment of pediatric HS. It should be noted that most biologic therapies are administered subcutaneously, which may be a barrier to adherence for some children [98]. Caregiver buy-in and an individualized approach may be necessary to administer these medications in needle phobic children [99]. Prior to the initiation of biologic immunomodulators, it is recommended to obtain baseline parameters including CBC with differential, complete metabolic panel, tuberculosis screening, hepatitis B and C screening, HIV screening, and signs/symptoms of infection or malignancy. Due to their activity as immunomodulators, these biologic therapies have been associated with increased susceptibility to infections, reactivation of hepatitis B, and development of active tuberculosis. So far, there are three main classes of biologic treatments used in the treatment of pediatric HS: TNF-alpha inhibitors, IL-17 inhibitors, and IL-12/23 inhibitors (see Table 4); however, with the development of more biologic therapies, the options are likely to grow in the future.

5.1 TNF-Alpha Inhibitors

TNF-alpha inhibitors have been successful in the treatment of many inflammatory conditions ranging from rheumatoid arthritis to inflammatory bowel disease, and psoriasis. More recently, they have been investigated and used in the treatment of HS. Adalimumab is the only biologic approved in the USA and Canada for the treatment of adults with HS, and adolescents aged 12–17 with HS. The indication for the treatment of adult HS is following the PIONEER-1 and PIONEER-2 randomized, placebo-controlled trials [100]. These trials, published in 2016, concluded that adalimumab resulted in significantly higher clinical response rates at 12 weeks compared with placebo, with similar rates of serious adverse events [100]. Further studies of pooled results showed that those who had at least partial response at 12 weeks were likely to continue to find benefits with weekly dosing during the subsequent 24 weeks [101]. It is important to note that these studies only included adults with HS; the approval for the indication of adalimumab for the treatment of pediatric HS stemmed solely from pharmacokinetic/pharmacodynamic modelling and simulation as there are no clinical trials with adalimumab in adolescent HS [102, 103]. Despite the lack of randomized controlled trials, there are numerous case reports of successful treatment of pediatric HS with adalimumab [90, 104, 105]. In several reports, adalimumab was the most commonly used biologic therapy followed by infliximab, another TNF-alpha inhibitor [97, 105]. Infliximab is not approved for the treatment of HS; however, smaller placebo-controlled studies and case series demonstrate that it may also be another effective option [3, 4, 104, 106]. Although TNF-alpha inhibitors are considered safe, their use has been associated with new-onset or worsening heart failure and malignancy [102]. Of all the biologics, clinicians may be most comfortable prescribing TNF-alpha inhibitors due to their long-term safety data for use in pediatric patients with other conditions [107].

5.2 IL-17 Inhibitors

Like TNF-alpha inhibitors, IL-17 inhibitors are monoclonal antibodies that have been used to successfully treat rheumatologic and dermatologic conditions in both adults and children. Although not currently approved in Canada or the USA for the treatment of HS, the SUNSHINE and SUNRISE randomized, placebo-controlled trials have recently demonstrated that secukinumab was clinically effective at rapidly improving signs and symptoms of HS with sustained response up to 52 weeks of treatment [108]. Although these patients were adults over the age of 18, this trial is important for the treatment of pediatric HS as it validates the role of IL-17A in the pathogenesis of the disease, and it is the first step towards expanding the indication to the pediatric population and it potentially paves the way for other IL-17 inhibitors to investigate their role in the treatment of HS. In addition, another phase 2 trial in adults has demonstrated that bimekizumab, an IL-17A and IL-17F inhibitor, was effective and safe in the treatment of moderate to severe HS at 12 weeks of treatment, further bolstering the future of IL-17 inhibitors as a treatment option for HS patients [109]. Further phase 3 trials with various IL-17 inhibitors are ongoing. Prior to these trials, there have been several small open-label trials and case reports demonstrating successful treatment of adults with HS with IL-17 inhibitors including secukinumab, ixekizumab, and brodalumab [110–113]. It should be noted that IL-17 inhibitors have been shown to exacerbate or increase the risk of developing inflammatory bowel disease, therefore patients with HS who have concomitant inflammatory bowel disease should not use IL-17 inhibitors [114].

5.3 IL-12/23 Inhibitors

IL-23 inhibitors and IL-12/23 inhibitors are monoclonal antibodies targeting cytokines involved in inflammatory conditions with agents approved for adult and pediatric dermatologic conditions in Canada and the USA. Ustekinumab is an IL-12/23 inhibitor that is approved for adult and pediatric psoriasis and psoriatic arthritis and has been used in the treatment of HS in adults. In various trials of adults with HS treated with ustekinumab, the majority of patients had clinical improvements in the modified Sartorius score,

Hidradenitis Suppurativa Clinical Response score (HiSCR), Dermatology Life Quality Index (DLQI), and Visual Analogue Scale (VAS) of pain with 16 weeks of treatment [112, 115, 116]. Two case studies report on the use of ustekinumab in two pediatric patients; however, there are no trials formally investigating its use.[117, 118]

IL-23 inhibitors use in the treatment of HS is not as promising as there are more conflicting results as more well-conducted trials are being published. Several case reports and an open-label phase II study have shown that guselkumab may be an effective option for adults with moderate-to-severe HS, with up to 65% of patients achieving HiSCR [119, 120]. However, a more recent phase 2 trial conducted in 243 adults failed to demonstrate risankizumab's efficacy in the treatment of moderate-to-severe HS [121]. This further confounds the utility of IL-23 inhibitors in the treatment landscape of HS.

5.4 Other Biologics

Several other biologics from various classes have been used for the treatment of pediatric HS, including etanercept, golimumab, and anakinra [97, 105]. There are too few data in adults, and especially in children to make any conclusive statements about their use in the treatment in children and adolescents with HS.

6 Conclusion

This review outlines the available evidence for the pharmacologic treatment of pediatric patients with HS. As an overview, the armamentarium of treatments includes topical treatments, systemic medications, and biologic therapies. Each of these treatments has a role to play depending on patient comorbidities, patient preferences, and disease severity. The available evidence in the pediatric population is significantly limited compared with adults, which can make decisions around treatment more challenging. The current practice of extrapolation of efficacy results from adult data and extrapolation of safety data from the treatment of other pediatric conditions is not ideal; further advocacy work is necessary to further explore the efficacy, safety, and monitoring of these treatments specifically in the treatment of pediatric HS.

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