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Recent advances in hidradenitis suppurativa in pediatrics

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Abstract
Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that can cause significant physical, mental, and socioeconomic burden. There remains a paucity of literature on HS in the pediatric population. This systematic review highlights recent advances in pediatric HS in epidemiology, presentation, comorbidities, and management. PubMed, Embase, Google Scholar, and Clinicaltrials.gov databases were used to identify trials and articles published on HS in pediatric patients between January 2015 and October 2019. A total of 39 articles were included. Current evidence suggests that pediatric onset HS may be associated with genetic factors along with endocrine and metabolic abnormalities. Delayed diagnosis in children with HS contributes to poor outcomes. Overall, children and adults with HS share similar lesion types and involved areas. Pediatric HS is associated with a number of comorbid conditions including acne, obesity, inflammatory joint disease, Down syndrome, inflammatory bowel disease, and diabetes. There are currently no pediatric treatment guidelines. Adalimumab is approved for the treatment of moderate-to-severe HS in children 12 and older. Other targeted immunomodulators and hormonal modulators are under investigation. Although the number of studies concerning HS are increasing, further investigation is warranted to better characterize HS, facilitate early diagnosis, and determine the best management for children.

Keywords: hidradenitis suppurativa, pediatric, childhood, children, adolescents, early onset

Introduction
Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that manifests as painful, deep-seated nodules, abscesses, sinus tracts, and scarring. The pathogenesis of HS has not been fully elucidated, but is believed to be a constellation of genetic factors, immune dysregulation, hormonal imbalance, and lifestyle factors [1].

Hidradenitis suppurativa is predominantly a disease of adulthood with typical onset in the second and third decades of life; however, the prevalence of pediatric onset HS is unknown. Thus, pediatric HS is a significant entity that cannot be overlooked. Children are a vulnerable population and those with chronic disease may face longstanding physical and psychosocial impairment. Prioritizing pediatric studies in HS may help promote early diagnosis, facilitate appropriate management, and ultimately decrease overall disease burden. Recent studies show an increase in the prevalence and incidence of pediatric HS [2,3]. However, the challenge of misdiagnosis and underdiagnosis remains, as HS patients often experience a diagnostic delay ranging from 7-14 years [4-6]. An editorial by HS experts suggests that early treatment of mild disease and incorporation of proactive disease modification into HS management can lead to improved outcomes [7].

A review published in 2015 outlined 12 cases of HS in the pediatric population and a treatment algorithm based on disease severity [1]. Since then, there have been advancements in the field of HS, including in
pediatric HS. This review aims to examine updates in epidemiological data, comorbidities, and treatment of HS in children.

**Methods**

A literature search was performed using PubMed, Embase, and Google Scholar databases in October 2019 for articles published between January 2015 and October 2019. MeSH search terms for PubMed and Embase were “hidradenitis suppurativa AND (child OR infant OR pediatric*)” NOT review", and “hidradenitis suppurativa AND (child OR infant OR pediatric*)” AND treatment." Search criteria for Google Scholar was “hidradenitis suppurativa” + “pediatrics” + “epidemiology” or “topicals” or “antibiotics” or “treatments”. Only full-text articles were included for the purpose of this review. The search criteria yielded 429 results. After duplicates were removed, 54 were excluded for being abstract-only. Of those remaining, 127 were excluded because they were not written in English, not relevant for the pediatric population, or not focused on HS (Figure 1). Review articles and studies that did not report percent of participants <18 years of age were also excluded. Ongoing and recently completed HS trials were searched using “hidradenitis suppurativa” in the “condition or disease section” in the clinicaltrials.gov database.

**Epidemiology**

As recent as 2017, the prevalence of pediatric HS was not known [8]. Since then, a number of published studies from the United States, Italy, Brazil, Portugal, Japan, and Korea have evaluated the epidemiology of pediatric HS (Table 1).

In the largest epidemiologic HS study to date (N=47,690), Garg et al. presents a sex- and age-adjusted U.S population analysis which identified 1,020 (2.2%) individuals between the ages 0-17 with HS. The standardized prevalence was 0.015%, which is significantly less than in adult age groups. Within this pediatric group, 0.014% were Caucasian, 0.01% were African American, and 0.007% were biracial [2]. In another report, Garg et al. reports the one-year cumulative incidence of pediatric HS to be 0.01% [3].

![Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)diagram.](image)

Braunberger et al. noted that boys (58.3%; N=7) are more likely than girls (41.7%; N=5) to develop HS in the prepubescent period (P=0.02). The reason for this pediatric distribution is unknown. The authors theorize that the rise in ovarian hormones such as estrogen and progesterone in the pubescent and postpubescent period contribute to the later female dominant distribution in adult HS populations. One theory for prepubertal pediatric HS involves the elevated conversion of testosterone to dihydrotestosterone in both males and females (hence the role for finasteride as a therapeutic strategy), [9]. However, there have been no large scale, age-adjusted studies to further investigate gender ratios in pediatric HS [10].

Santos et al. reports that HS-related hospitalizations are increasing and this is largely related to underdiagnosis and delay in treatment. Of 1,177 hospitalized patients, 4.1% were 18 years or younger, 0.7% were 14 years or younger, and 0.2% were 11 years or younger. Although the majority of hospitalized patients were in their 20s and 30s, initial symptom onset was typically between the ages of 5-
Table 1. Epidemiology of hidradenitis suppurativa by geographic regions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Pertinent Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garg et al. [3]</td>
<td>United States</td>
<td>Pediatric prevalence is 0.028%. HS incidence has increased, with a 1-year cumulative incidence of 0.01%. Prevalence and incidence are likely underrepresented.</td>
</tr>
<tr>
<td>Braunberger et al. [10]</td>
<td>United States</td>
<td>3.8:1 ratio of girls to boys in pediatric HS. Boys are more likely to contract HS than girls in the prepubescent period. Mechanism is largely unknown; however, the authors theorize that ovarian androgen involvement may have greater role of adult HS pathogenesis than in prepubescent disease.</td>
</tr>
<tr>
<td>Bettoli et al. [16]</td>
<td>Italy</td>
<td>Of 235 patients, 90 had disease onset prior to the age of 16 years; of which, 15 had disease onset prior to puberty. 2.2:1 F/M ratio and 33 had a positive family history of HS. Localization of initial disease onset was as follows: inguinal-crural (39), axillary (26), gluteus or intergluteal (11), and mammary (7).</td>
</tr>
<tr>
<td>Andrade et al. [49]</td>
<td>Brazil</td>
<td>19.5% of patients were diagnosed between the age of 10-19 years old. There were no reported patients between the ages of 0-9 years. Patient characteristics were not stratified by the pediatric population.</td>
</tr>
<tr>
<td>Yang et al. [50]</td>
<td>Korea</td>
<td>Of 438 patients, 49% of all surveyed developed HS between the ages of 0-19, 209 of which developed HS between the ages of 10-19 years and 6 of which were between the ages of 0-9. Patient characteristics were not stratified by the pediatric population.</td>
</tr>
<tr>
<td>Kurokawa et al. [51]</td>
<td>Japan</td>
<td>Reports 8 individuals (6M/2F) ages 10-19 that self-reported their diagnosis of HS. Disease characteristics, such as location, years affected, severity, family history, associated disease/factors, or treatment were not stratified by age.</td>
</tr>
<tr>
<td>Santos et al. [11]</td>
<td>Portugal</td>
<td>Hospital incident rate of 0.83 patients per 100,000 person-years. Over a 14-year period, 1,177 patients were determined to be hospitalized with HS as a primary (76.1%) or secondary (23.9%) diagnosis. Patients were typically in their 20s and 30s and there were over 70 patients newly diagnosed with HS that were between the ages of 5 and 19. Hospitalization rates are increasing, and HS is a largely underdiagnosed and undertreated condition.</td>
</tr>
<tr>
<td>Ianhez et al. [52]</td>
<td>Brazil</td>
<td>In 6048 residencies (17,004 inhabitants) surveyed, ~0.09% of the population less than 12 years of age had HS.</td>
</tr>
</tbody>
</table>


Clinical presentation
Prior to this systematic review, there were only 12 reports of pediatric HS in the literature [1]. This systematic review yielded 62 total pediatric patients (18 males, 44 females), (Table 2). Within this cohort, age of disease onset ranged from birth to 17 years of age. Patients with congenital nevus comedonicus had the earliest age of onset, with HS lesions apparent at birth. Positive family history of HS was reported in only a minority of cases. The following outlines a summary of the clinical presentations of the 62 pediatric patients that resulted from our search.

Patients with pediatric HS presented to clinic at varying degrees of disease severity, often related to diagnostic delay and inappropriate treatment regimens. The most common clinical presentation was single, recurrent inflammatory nodules in the axillae, groin, anogenital region, and buttocks. In some cases, patients presented with open comedones alone. Other documented lesion-types include pustules, pseudocysts, ulcerations, and abscesses with purulent drainage. Areas with minimal disease involvement included the mammary region, thighs, trunk, face, inguinal region, and postauricular region.

Children and adults share similar lesion types and affected areas. However, pediatric onset of HS may be more associated with endocrine and metabolic abnormalities such as concomitant adrenal hyperplasia, obesity, or precocious puberty [12]. These associations are derived only from case reports and case series and thus further studies are
warranted to clarify statistical associations, as there may be a bias of reporting those cases with rare associations.

Comorbid conditions
In this systematic review, a number of comorbid conditions were associated with pediatric HS including acne, obesity, inflammatory joint disease, Down syndrome, inflammatory bowel disease, and diabetes. There are case reports of more rare diseases associated with pediatric HS, such as Darier disease, PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis)/PAPASH (pyogenic arthritis, acne, pyoderma gangrenosum, and suppurative hidradenitis), Dent disease type two (DD2), (a genetic kidney disorder with associated intellectual disability, hypotonia, and cataracts), and multiple self-healing palmoplantar carcinoma (MSPC).

Although pediatric HS literature is limited compared to adult HS, there has been an increase in reported comorbid conditions with pediatric HS. The following section outlines reported comorbidity associations between 2015–2019.

Somatic comorbid conditions
Shavit et al. reported somatic comorbidities were significantly higher in children with HS (34.0%) compared to controls (4.9%), [13]. Acne was the most prevalent comorbidity (13.7%), followed by obesity (5.9%), inflammatory joint diseases (5.2%), Down syndrome (DS) (4.6%), inflammatory bowel disease (3.3%), diabetes (2.6%), thyroid disorders (2.6%), hypertension (2.0%), metabolic syndrome (2.0%), and pilonidal sinus (1.3%).

Acne
Acne is a common skin condition that results from plugging of hair follicles. Recent reports of acne in pediatric HS patients are limited to cases of PASH and PAPASH syndromes. Duchatelet et al. presented a 14-year-old boy with a strong family history of acne that developed acne fulminans following the rapid onset of severe HS of the buttocks and groin. The patient also had localized pyoderma gangrenosum of the sternum and thighs. Additionally, there was a case of an 11-year-old girl with severe HS with subsequent onset of severe acne and extensive pyoderma gangrenosum of the limbs and trunk [14].

Obesity
In a cross-sectional age- and sex-controlled study, Shalom et al. evaluated 3,207 HS patients for correlations with diabetes, hyperlipidemia, obesity, hypertension, and metabolic syndrome. There were no statistically significant correlations in the six patients with HS between the ages of 1-10. However, for patients aged 11-20, there was a significant correlation between HS and obesity (body mass index >30 kg/m²), (P=0.005). Additionally, Andersen et al. (N =195) found that 2.6% (N=5) of overweight or obese pediatric patients had HS [15]. However, a cross-sectional study by Bettoli et al. demonstrated that individuals with HS less than 18 years of age were less likely than adults to be overweight or obese (age-standardized prevalence ratio 1.4, 95% CI 1.1–1.9), [16].

Inflammatory joint disease
A case report published prior to 2015, describes a 16-year-old girl with diagnosed PAPASH syndrome with polyarthritis. She demonstrated partial remission after treatment with anakinra [17]. In this particular patient, a p.E277D missense mutation in the PSTPIP1 gene (coding for proline-serine-threonine phosphatase-interacting protein 1) resulted in increased CCTG microsatellite repeats in the PSTPIP1 5’UTR region. This mutation is believed to increase aggregation of inflammasomes and activate IL1β, which leads to neutrophilic inflammation and aseptic abscess formation [17].

Since then, another case reported an NCSTN glycoprotein mutation in a PASH patient. The NCSTN gene is directly implicated in HS, as it codes for a type I transmembrane glycoprotein of the γ-secretase complex [14]. These deficiencies result in impairment of the Notch signaling pathway, inhibition of Toll-like receptor activated macrophages, and inhibition of mitogen-activated protein kinase-dependent cytokine production. This results in excess macrophage activation and increased production of proinflammatory cytokines. When there is abnormal keratinization of the hair follicle funnel and epidermal cyst formation, cyst rupture results in a severe inflammatory response.
**Down syndrome**

Prior to 2015, only a 1999 case report described an association between DS and HS; however, recent reports have also highlighted this association [18]. Increased amyloid precursor proteins (APP) in trisomy 21 patients demonstrate impaired notch signaling. At baseline, APP is responsible for producing cleavage products involved in keratinocyte adhesion, migration, and proliferation. When Notch signaling is abnormal, APP deposits interrupt normal keratinocyte function and have been hypothesized to trigger follicular plugging, the inciting event for HS [19].

Garg et al. performed a cross-sectional analysis of 11,936 patients with DS and 16,813,290 patients without DS and determined that the prevalence of HS was seven times higher (P<0.001) in patients with DS [20]. A 2017 observational prospective study found a 38% prevalence of HS among DS patients [19]. In a retrospective study involving 257 patients (mean age 23.3±10.7 years), Giovanardi et al. reported the prevalence of DS to be as high as 3.5% of HS cases and noted a significantly earlier age of HS onset in DS patients (mean age: 14.3±3.6 versus 23.4±12.31 years; P<0.05), [21]. Another retrospective chart review study reported 2.4% of their patient population had concomitant HS and DS and similar to Giovanardi et al., the study found a younger age of HS onset in DS patients [22]. Therefore, early screening for HS in DS patients is warranted.

**Inflammatory bowel disease**

In the last four years, there were 8 reported pediatric cases (ages range 2-18) of HS with concomitant Crohn disease (CD), [23,24]. The average age of CD and HS onset was 10.67 (range: 2-14) and 12.11 (range: 2-16) years, respectively.

Of the 8 reported pediatric cases, five were diagnosed with CD prior to their HS (average time period of 2.2 years). Alternatively, three had CD and HS diagnosed at the same age (ages 2, 11, and 12) and one did not report the age of onset of HS. The youngest reported case is an African American girl who developed perineal HS and colonic CD at age 2. She inadequately responded to anti-TNF (tumor necrosis factor) therapy and ultimately required surgical excision of HS lesions. The age at which her anti-TNF therapy failed was not reported. It is uncertain if the other seven HS/CD cases occurred in the pubescent period. Although there appears to be a link between HS and CD, further studies are necessary to elucidate mechanistic links [24].

**Psychiatric conditions**

Hidradenitis suppurativa patients have higher rates of psychiatric comorbidities. In a retrospective database study, Tiri et al. evaluated 153 cases of pediatric HS and found that significantly more HS patients have at least one psychiatric condition compared to age matched controls (15.7% versus 5.6%), [13]. Comorbid psychiatric illnesses included major depression (8.5%), anxiety disorders (5.9%), psychotic disorders (2.0%), and dissociative, stress-related, somatoform, and other nonpsychotic mental disorders (9.2%). The prevalence of mental illness increases as pediatric HS patients grow older, reaching 23.5% at 23 years old compared to 8.7% in controls [13].

In a cross-sectional study, Shavit et al. studied 9,619 patients under age 20 and reported a higher prevalence of depression (5.9% versus 3.5%) and anxiety (3.9 versus 2.4%) in those with HS compared to age- and sex-matched healthy controls [25]. These results were not statistically significant.

In a retrospective cohort study, Andersen et al. (N=195) reported that those with concomitant HS and obesity have higher levels of psychiatric comorbidities (P<0.0001), [15]. Specific psychiatric conditions were not stratified. Practitioners should be aware of existing and potential psychiatric comorbidities in the pediatric HS population.

**Other conditions**

Multiple self-healing palmoplantar carcinoma is an autosomal dominant condition presenting as multiple keratoacanthomas affecting non-hair-bearing epithelium (e.g. palms and soles). A gain-of-function nucleotide-binding domain, leucine rich family pyrin domain containing one (NLRP1) mutation leads to inflammasome hyperactivity, resulting in hypersecretion of IL1 and subsequent inflammation-induced skin hyperplasia and keratoacanthoma formation. It is hypothesized that
HS may be propagated secondary to MSPC as a result of autoinflammation and accentuated cytokine milieu (e.g. IL1β) caused by MSPC. Notably, IL1β, one of the primary inflammatory cytokines is implicated in HS [26].

Dairer disease is a rare, autosomal dominant condition caused by a mutation in the SERCA (sarcoplasmic reticulum calcium adenosine triphosphatase) gene on chromosome 12q23-24, that results in calcium imbalance. It presents with multiple, odorous, warty plaques that can occur in a variety of anatomical locations. With respect to HS, it is theorized that impairments in SERCA result in aberrant NOTCH signaling [27].

Dent disease type two (DD2) is a rare, X-linked disorder that is the result of proximal tubule dysfunction. It presents with kidney dysfunction, resulting in nephrocalcinosis, osteomalacia, and intellectual disability. Marzuillo et al. report cases of pediatric onset HS in DD2 patients, all of whom had single nucleotide changes resulting in missense mutations and abnormal OCRL1 protein function [28]. In DD2, predisposition to HS disease is unknown but may result from mutations leading to decreased OCRL1 activity, which is responsible for membrane trafficking and formation of primary cilium. Aberration in this protein may lead to an increased propensity to cutaneous infections [28].

Treatment and management
There have been significant advancements in pediatric HS treatment. The following section is a review of HS therapies in pediatric patients reported in the past 5 years. There are currently no pediatric treatment guidelines. First-line therapies commonly include topical and oral antibiotics, hair removal laser (Alexandrite, NdYAG), and intraleisional corticosteroids, followed by hormonal treatments and TNF inhibitors/surgery for recalcitrant cases. These therapies are largely extrapolated from adults and adopted for pediatric care.

TNF inhibitors
TNF inhibitors are monoclonal antibodies that directly bind to TNF and neutralize the effects of TNF, thus decreasing the inflammatory cascade implicated in HS [29]. TNF expression has been found to be 5-fold higher in active HS lesions than nonlesional skin. Other inflammatory cytokines, including IL1β, IL10, and IL17 have also been noted to be significantly elevated in HS lesional skin [30,31].

Adalimumab
In 2018, adalimumab was approved for the treatment of moderate-to-severe HS in children ages 12 and older. Adalimumab did not undergo phase 3 clinical trials for its pediatric indication. The adolescent indication was approved based on pharmacokinetic simulation and presumed similarities in the drug’s efficacy and safety profile between adolescents and adults [32,33]. Adalimumab has been trialed off-label in preadolescent children. Sahu et al. demonstrated significant improvement of HS-like lesions with the administration of adalimumab in a 6-year-old girl [34] who experienced recurrent abscess formation since birth. Comorbidities included oligodontia, bilateral cataracts, and supernumerary toes on bilateral feet. After failing multiple HS treatments (clindamycin/rifampicin, oral acitretin, and oral isotretinoin), she was treated with two courses of adalimumab, each consisting of a 40mg loading dose followed by an additional 40mg dose, every four weeks. She demonstrated sustained improvement with no HS flares in the following 6-month period [34].

In case series of seven patients with concomitant HS (age of onset between 10-15) and Crohn disease (age of onset between 9-15) treated with either infliximab or adalimumab, three had complete response whereas the other four needed surgical excision of their HS lesions. Duration of treatment for response was not reported [24].

Ustekinumab
Ustekinumab is an IL12/23 inhibitor reported effective in the treatment of HS [35]. Although not approved for children, one case report demonstrated its use. A 17-year-old girl was hospitalized for worsening, severe HS. She was recalcitrant to ustekinumab monotherapy, but demonstrated complete remission upon combination ustekinumab and hyperbaric oxygen
therapy (6 days/week for 6 weeks), [36]. Of note, ustekinumab is FDA approved for the treatment of adolescent (ages 12-17) psoriasis but not HS.

**Finasteride**

Finasteride is a competitive and selective inhibitor of 5α-reductase believed to improve HS. The precise mechanism of action is unknown. However, finasteride decreases levels of dihydrotestosterone, which is believed to have a localized effect on the hair follicle [37].

Finasteride for the treatment of pediatric HS was first reported in 1999 by Farrel et al. [38]. Comprehensively, nine pediatric cases including both male (1) and female (8) patients have reported using finasteride as a mono- or additive therapy for HS [38-43]. Most recently, a 2017 case series by Mota et al. showed that five postpubertal pediatric patients (age of onset range from 6-11) treated with finasteride (dosing ranging from 1-5mg/day) showed improvement with reduction in the frequency and intensity of flares [43]. Two patients were overweight (BMI 26 and 27), but did not require higher dosing. The remission period was variable, ranging from 5-24 months following the initiation of finasteride. Notably, two patients demonstrated new onset inflammatory lesions after stopping the treatment regimen. No side effects were noted from this treatment.

In prescribing finasteride, precautions are necessary, as the side effects in pediatric patients are not fully elucidated, per the FDA [44]. In men (ages 18-45), low dose finasteride has been associated with persistent sexual dysfunction (11.8%) and suicidal ideation (7.9%), [45]. Some authors recommend finasteride for short periods of time in severe refractory HS cases [46]. Finasteride is contraindicated during pregnancy and is not recommended as a monotherapy for women of reproductive age [37]. In rare instances, finasteride has been used in conjunction with oral contraceptives or other contraceptive methods to prevent pregnancy. Nevertheless, finasteride is a cost-effective, sustainable, and relatively safe option for select pediatric HS patients.

**Miscellaneous**

Recent studies have explored diagnostic ultrasound as a new method for diagnosis of pediatric HS. Wortsman et al. used ultrasound to examine children with HS, and revealed that 11 of 12 patients had more severe disease (e.g. multiple fluid collections, fistulas) than clinically evident. Notably, ultrasonographic use did not lead to increased rate of biologic or surgical interventions.

**On the Horizon**

Longitudinal Observational Study of Patients Undergoing Therapy for IMISC (TARGET-DERM) is a 5-year observational study that aims to create a registry of adult and pediatric patients affected by immune mediated inflammatory skin conditions (IMISC) and evaluate current and future therapies [47]. Although there are no additional trials specifically addressing pediatric HS, future biologic studies will seek pediatric indication following approval in adult HS populations.

**Discussion**

Although there have been advances in pediatric HS, significant genetic, clinical, and therapeutic gaps remain in the literature. It is theorized that genetic factors are one of the leading causes of HS. Genes implicated in the development of HS include PSEN1, PSENEN, and NCSTN, which each comprise the γ-secretase complex [1]. Despite being implicated in a minority of HS cases, the role of γ-secretase mutation is well-documented in HS kindreds [48]. However, the development of HS is not limited to γ-secretase mutations and specific investigation into pediatric HS genetics is warranted. Prediction of HS development based on genetics is not yet available but should be a future investigative direction.

Although recent studies have attempted to elucidate pediatric clinical associations, the full spectrum is yet to be explicated. Specifically, large scale studies stratifying the various presentations of pediatric HS and subsequent progression are needed. Comorbidities, such as acne, obesity, inflammatory bowel disease, and inflammatory joint disease, should also be further investigated.
As the efficacy and safety profiles of various biologics become available, pediatric indications will be sought out. Currently, there are two active clinical trials addressing pediatric HS, TARGET-DERM and Trial Comparing Efficacy of Treatments for Hidradenitis Suppurativa. However, further clinical trials are anticipated in the future.

Diagnostic delay is common among pediatric HS patients. By the time patients receive care from a dermatologist or pediatric dermatologist their disease state may be advanced. Increased awareness and pediatric-specific HS guidelines are necessary to counter underdiagnosis and mismanagement of pediatric HS patients. As the foundation of literature increases for this condition, providers will be better equipped to diagnose, manage, and educate their patients.

Conclusion
Hidradenitis suppurativa is a complex immunologic skin disease with a wide range of comorbidities. Pediatric HS may be an underreported condition and early diagnosis and aggressive treatment are necessary to mitigate disease burden. This review examines reports in the last four years that characterize pediatric HS, including its epidemiology, select comorbidities, and therapeutic trials. There is a dearth of studies addressing pediatric HS pathogenesis, comorbid conditions, and therapeutic options, highlighting the disparity between pediatric and adult HS advances. Looking forward, additional randomized clinical trials examining immunomodulators, hormonal modulators, and antimicrobial therapies are warranted. Pediatric-specific guidelines and clinical phenotyping are necessary to better manage pediatric HS and optimize care for this particularly vulnerable patient population.

Potential conflicts of interest
Dr. Rundle has a salary funded by Pfizer Independent Grants for Learning and Change (PI: RP Dellavalle): Inflammatory and Immune-mediated Skin Disease Fellowship. Dr. Shi is a stock shareholder of Learn Health and has served as an advisory board member, investigator, and/or received research funding from Sanofi Genzyme, Regeneron, AbbVie, Eli Lilly, Novartis, SUN Pharma, LEO Pharma, Pfizer, Menlo Therapeutics, Burt’s Bees, LearnHealth, GpSkin and Skin Actives Scientific. There were no incentives or transactions, financial or otherwise, relevant to this manuscript. Dr. Hogeling has been an investigator for Celgene (not relevant to this manuscript). Miss Price and Dr. Hsiao have no conflicts of interest to declare relevant to this manuscript.

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31. van der Zee HH, de Ruiter L, van den Broecke DG, Dik WA, Laman JD, Prens EP. Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNFα and IL1β. Br J Dermatol. 2011;164:1292-1298. [PMID: 21332464].


Table 2. Pediatric case studies or series of hidradenitis suppurativa patients reported in the literature between 2015–2019.

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Author(s), year</th>
<th>Sex</th>
<th>Age of onset (yr)</th>
<th>Family history</th>
<th>Lesion type</th>
<th>Location</th>
<th>Associated conditions</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Study</td>
<td>Duchatelet et al., 2015 [14]</td>
<td>F</td>
<td>11</td>
<td>Unknown</td>
<td>Not reported</td>
<td>Not reported</td>
<td>PASH (acne fulminans and pyoderma gangrenosum specifically)</td>
<td>Not reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Case Study</td>
<td>Lopes et al., 2019 [53]</td>
<td>F</td>
<td>10</td>
<td>N/A</td>
<td>Inflammatory nodules, fistulous submucosal pathways</td>
<td>Perianal, vulva</td>
<td>N/A</td>
<td>Adalimumab</td>
<td>Marked improvement</td>
</tr>
<tr>
<td>Case Study</td>
<td>Morand et al., 2019 [54]</td>
<td>M</td>
<td>14</td>
<td>N/A</td>
<td>Inflammatory nodules, abscesses, sinus tracts</td>
<td>Buttock, thigh, axilla</td>
<td>Normal, no evidence of androgen excess</td>
<td>Silver-coated textile (polyamide and elastan) boxer briefs</td>
<td>Significant reduction of number and size of inflammatory nodules and papules</td>
</tr>
<tr>
<td>Case Study</td>
<td>Oranges et al., 2018 [55]</td>
<td>F</td>
<td>10</td>
<td>N/A</td>
<td>Inflammatory nodules, noninflamed nodules, scarring</td>
<td>Axillae, sternum, inguinal regions, submammary folds</td>
<td>Acne vulgaris, depression, bulimia, pilonidal cyst.</td>
<td>Adalimumab, ND-YAG laser, and CO2 laser</td>
<td>Almost complete remission of active disease, improved quality of life, reduction of scar tissue.</td>
</tr>
<tr>
<td>Case Study</td>
<td>Ornelas et al., 2016 [27]</td>
<td>F</td>
<td>16</td>
<td>Not reported</td>
<td>Inflammatory nodules</td>
<td>Face, trunk</td>
<td>Darier disease</td>
<td>Isotretinoin</td>
<td>Not reported</td>
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<tr>
<td>Case Study</td>
<td>Ornelas et al., 2016 [27]</td>
<td>F</td>
<td>16</td>
<td>Not reported</td>
<td>Inflammatory nodules</td>
<td>Axillae, buttocks, groin</td>
<td>Darier disease</td>
<td>Isotretinoin and blue-light photodynamic therapy</td>
<td>“Effective”</td>
</tr>
<tr>
<td>Case Study</td>
<td>Provini et al., 2019 [36]</td>
<td>F</td>
<td>13</td>
<td>Not reported</td>
<td>Inflammatory nodules with ulcerations</td>
<td>Bilateral axilla, inframammary region, sternum, groin, gluteal cleft</td>
<td>Depression, Restrictive eating disorder with severe malnutrition</td>
<td>Ustekinumab, hyperbaric oxygen therapy</td>
<td>Complete remission</td>
</tr>
<tr>
<td>Case Study</td>
<td>Ravaioli et al., 2018 [56]</td>
<td>F</td>
<td>9</td>
<td>N/A</td>
<td>Inflammatory Nodule</td>
<td>Right axilla</td>
<td>Congenital nevus comedonicus</td>
<td>Surgical excision</td>
<td>Complete remission</td>
</tr>
<tr>
<td>Case Study</td>
<td>Author et al., Year [Reference]</td>
<td>Gender</td>
<td>Age</td>
<td>Presenting Features</td>
<td>Clinical Diagnoses</td>
<td>Treatment</td>
<td>Outcome</td>
<td></td>
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<tr>
<td>Case Study</td>
<td>Scheufele et al., 2019 [26]</td>
<td>F</td>
<td>16</td>
<td>Ulcerated abscess with active purulent drainage</td>
<td>Axillae, groin, anogenital region</td>
<td>Normal, no evidence of androgen excess</td>
<td>Incision and drainage</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Case Study</td>
<td>Schulman et al., 2015 [57]</td>
<td>F</td>
<td>8</td>
<td>Polyporous comedones, red papules, inflammation nodules, and atrophic scarring</td>
<td>Groin</td>
<td>Normal, no evidence of androgen excess</td>
<td>Oral isotretinoin, topical 20% azelaic acid cream</td>
<td>Complete remission</td>
<td></td>
</tr>
<tr>
<td>Case Study</td>
<td>Stojkovic-Filipovic et al., 2015 [58]</td>
<td>F</td>
<td>8</td>
<td>Not reported</td>
<td>Double-ended pseudocomedones</td>
<td>Genitofemoral region</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Case Series (11 patients)</td>
<td>Hamadah et al., 2017 [19]</td>
<td>8M / 3F</td>
<td>14.8 (Average)</td>
<td>N/A for all cases</td>
<td>Variable</td>
<td>Down syndrome (11/11)</td>
<td>Minocycline (7/11), doxycycline (2/11), isotretinoin (1/11), topical clindamycin (1/11)</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Case Series (1 pediatric patient)</td>
<td>Lacanubba et al., 2016 [59]</td>
<td>F</td>
<td>8</td>
<td>Not reported</td>
<td>Inflammatory nodules developed into abscesses, fibrosis</td>
<td>Axillae, groin, mammary, inframammary, and trunk</td>
<td>Topical clindamycin and benzoyl peroxide (4/4), oral lymecycline (4/4), oral minocycline (3/4), oral isotretinoin (1/4), adalimumab (2/4)</td>
<td>Improvement (2/4), No improvement (2/4)</td>
<td></td>
</tr>
<tr>
<td>Case Series (6 patients)</td>
<td>Mota et al., 2017 [43]</td>
<td>1M / 4F</td>
<td>8.4 (Average)</td>
<td>Acne (1/5)</td>
<td>Inflammatory nodules, scarring</td>
<td>Not reported</td>
<td>Obesity (2/5)</td>
<td>Oral finasteride (5/5)</td>
<td>Improvement (5/5)</td>
</tr>
<tr>
<td>Case Series (7 patients)</td>
<td>Natarajan et al., 2015 [24]</td>
<td>7F</td>
<td>11 (Average)</td>
<td>Diverticulitis (1/7)</td>
<td>Inflammatory nodules and scarring</td>
<td>Axillae (5/7), perineum (5/7), trunk (2/7), vulva</td>
<td>Crohn disease (7/7)</td>
<td>Infliximab or adalimumab (7/7)</td>
<td>Complete remission (3/7), partial response</td>
</tr>
<tr>
<td>Study Type</td>
<td>Authors</td>
<td>Gender</td>
<td>Age (Years)</td>
<td>Race</td>
<td>Histories</td>
<td>Lesions</td>
<td>Treatment</td>
<td>Outcome</td>
<td></td>
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<tr>
<td>Retrospective Study</td>
<td>Kamal et al., 2016 [23]</td>
<td>M</td>
<td>16</td>
<td></td>
<td>No history of inflammatory bowel disease</td>
<td>Axillae, buttocks, anogenital region</td>
<td>Crohn disease</td>
<td>Antibiotics, intralesional steroids, intralesional tacrolimus, right axilla excision</td>
<td>Not reported</td>
</tr>
<tr>
<td>Retrospective Study</td>
<td>Offidani et al., 2019 [9]</td>
<td>F</td>
<td>8.12 (Average)</td>
<td></td>
<td>HS (2/8)</td>
<td>Variable</td>
<td>Inguinal region, anogenital regions, axillae</td>
<td>Overweight/obese (8/8), hyperandrogenism (2/8), concomitant precocious puberty and hyperinsulinism (1/8)</td>
<td>Oral azithromycin, oral zinc, topical clindamycin</td>
</tr>
<tr>
<td>Retrospective Study</td>
<td>Wortsman et al., 2016 [60]</td>
<td>M/F</td>
<td>11.6 (Average)</td>
<td></td>
<td>Not reported</td>
<td>Fluid collections, fistulas, hair tracts, pseudocysts</td>
<td>Axillae (6/12), groin (10/12), perineum (1/12), scrotum (1/12)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Fractions indicated in parentheses represent the proportion of study participants with the reported family history, lesion location, associated conditions, treatment, or outcome.