REVIEW ARTICLE

Bullous Diseases in Children: A Review of Clinical Features and Treatment Options

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Abstract

Bullous diseases are uncommon in children; however, as they have the potential to affect quality of life, occasionally have long-term side effects in the setting of scarring processes, and carry a rare risk of underlying malignancy [e.g., with paraneoplastic pemphigus (PNP)], knowledge of their clinical presentation and treatment options is essential. Given the rarity of these conditions, our current state of knowledge is largely derived from case reports and case series, with a paucity of evidence-based recommendations. In this review, we discuss the clinical presentation of and treatment options for linear immunoglobulin A disease, dermatitis herpetiformis, pemphigus vulgaris, pemphigus foliaceus, PNP, bullous pemphigoid, mucus membrane pemphigoid, epidermolysis bullosa acquisita, and inherited epidermolysis bullosa. In general, when these conditions, except for PNP, occur in childhood, they have a better prognosis than when they occur in adults. Clinical, histopathological, and immunologic features frequently overlap, but distinct differences have also been reported, most commonly in clinical presentation. Treatment is often similar to that in adults, although specific considerations are necessary for a pediatric population.

Key Points

Immunobullous and inherited bullous conditions are rare in children but can result in significant morbidity.

Distinct clinical presentations of bullous conditions have been reported in neonatal, infantile, childhood, and juvenile populations.

When considering treatment options in pediatric populations, long-term consequences must be considered.

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1 Introduction

Both immunobullous and inherited bullous conditions are—overall—uncommon in children. Given this low prevalence, the true incidence of immunobullous diseases is difficult to assess. Dermatology referral centers from US and Singapore populations noted just 23 and 12 cases, respectively, of pediatric immunobullous diseases over approximately 15 years, with the most common diagnoses being dermatitis herpetiformis (DH) in the US population [1] and linear immunoglobulin A (IgA) bullous dermatosis (LABD) [2] in the Singapore population. Misdiagnosis was common, particularly overdiagnosis of DH and mistaking pemphigus foliaceus (PF) or LABD for bacterial impetigo [1]. In cases of inherited bullous conditions, such as epidermolysis bullosa (EB), national registries allow a more precise estimate of incidence, recently found to be approximately 19 per 1 million live births [3]. Although pediatric bullous diseases are relatively infrequent, they create a significant financial burden and affect quality of life (QOL). Pemphigus is the most common pediatric autoimmune blistering disease (AIBD) with a primary admission [4], and recessive dystrophic EB (RDEB) has profound effects on QOL and economic burden [5].

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When considering a diagnosis of pediatric bullous disease, infection is often the more likely etiology and may be more immediately life threatening so must be ruled out. Once infectious causes have been excluded, diagnosis can be challenging because of the frequent clinical and histopathologic overlap of many pediatric bullous diseases, thus necessitating careful review of immunologic features. In general, recommendations for treatment options are limited because of the overall rarity of conditions and the lack of controlled trials. We discuss the clinical presentation and treatment of several key bullous diseases in children, with an emphasis on how they differ from those in adults. We also note specific differences among the various pediatric populations, such as the neonatal, infantile, childhood, and juvenile populations, when known. Lastly, we discuss special considerations for treatment of bullous diseases in the pediatric population.

2 Immunobullous Conditions

2.1 Linear Immunoglobulin A Bullous Dermatosis

LABD is an immunobullous, subepidermal eruption that occurs in two distinct forms in adults and children. In adults, it frequently mimics bullous pemphigoid (BP) or DH but has distinct immunologic findings, including linear deposition of IgA along the basement membrane zone (BMZ) and circulating IgA antibodies to a variety of antigens, most often identified as the 97- and 120-kD portions of BP antigen 2 (BPAG2 or BP180). Additionally, other mimics have been described, including Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), prurigo nodularis, and gyrate erythema-like LABD [6].

When LABD occurs in children, it is called chronic bullous disease of childhood (CBDC) and has classically been described as tense blisters in an annular or rosette pattern ("crown of jewels" or "string of pearls") (Fig. 1). The cutaneous lesions are more generalized in adults but in children favor the lower abdomen, thighs, genital, and perioral areas [7]. Mucosal involvement has been reported in both adults and children, occasionally with scarring, although these original reports with scarring may have been more fitting with mucous membrane pemphigoid (MMP), which can be difficult to distinguish from LABD [8]. The mean age of onset in children is 4.5 years [8], and the clinical course is more benign than in adults, as exemplified by a shorter duration of disease (mean 3.9 and 5.6 years in children and adults, respectively) and fewer relapses [7]. Persistence of disease into adulthood has been reported in a minority [8]. Immunologic findings and thus diagnosis in children are the same as in adults.

In the adult literature, LABD has been reported to be drug induced, with vancomycin as the most frequent culprit [6].

Fig. 1 Linear immunoglobulin A bullous dermatosis

In adult cases of vancomycin-associated LABD, type VII collagen has recently been identified as a target antigen. Furthermore, this autoreactivity has been shown to be mediated by effects of vancomycin on IgA via an unknown mechanism [9]. Fewer cases of drug-induced LABD have been reported in children, with one report of amoxicillin–clavulanic acid leading to development of CBDC that remitted with cessation of the medication [10]. Such reactions to amoxicillin, minocycline, and vibramycin have also been reported [11]. Additionally, in a report on patients with CBDC, childhood cicatricial pemphigoid, and adult LABD, 31% of patients had received nonsteroidal anti-inflammatory drugs or antibiotics before the eruption, but no further details on which groups took these medications are provided [8]. In this same series, 38% of the children and 26% of the adults had a preceding infection [8].

Associations between LABD and underlying diseases in adults, such as hematologic malignancies, ulcerative colitis, and autoimmune conditions, have also been reported in the literature [6]. Fewer reports exist for underlying disease associations in pediatric patients, but CBDC has been reported in the setting of ulcerative colitis [12] and autoimmune lymphoproliferative syndrome [13]. Additional reports of CBDC are cofounded by the presence of a potential underlying condition and medication exposure, such as that of a child with acute lymphoblastic leukemia in remission [14] and a child with idiopathic congenital thrombocytopenia presenting with cytomegalovirus infection, both of whom developed CBDC after receiving trimethoprim–sulfamethoxazole [15]. In the latter case, the child again developed cutaneous findings upon rechallenge with trimethoprim–sulfamethoxazole.

LABD in neonates presents with important distinctions from other bullous diseases. In a recent systematic review of 51 cases of neonatal AIBDs, of which five were LABD and one was a dual diagnosis of LABD and BP, onset of symptoms after birth was later in LABD, maternal disease or symptoms were absent during pregnancy, and the overall prognosis was worse, with a propensity for oral, esophageal, and laryngeal lesions and a need for systemic therapy [16]. The absence of maternal disease, which is striking compared with the frequent involvement in other bullous diseases, is postulated to be due to the slower transfer of IgA across the placenta, although maternal status was unreported in three of the neonatal LABD cases [16].

As we discuss for all bullous diseases in children, definite treatment recommendations are lacking because of the rarity of cases and lack of randomized controlled trials. Thus, recommendations are largely based on case reports, case series, and expert opinion (Table 1). Overall, LABD treatment in adults and children does not vary significantly, other than special considerations for the pediatric population. The drug of choice is dapsone, initially 0.5 mg/kg/day and gradually increased until symptom control (usually 2 mg/kg/day) [17]. Sulfapyridine has also been used, although it is not available in the USA except possibly under cases of compassionate use. Adjunct corticosteroids can be used in the short term but should generally be avoided in children because of its side-effect profile with long-term use. Colchicine, usually 0.6 mg twice daily, can be considered for patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or who are otherwise intolerant to dapsone or sulfapyridine. Antibiotics, including erythromycin, dicloxacillin, and oxacillin, may be beneficial in CBDC, but tetracyclines are not recommended in children aged < 8 years because of the risk of permanent tooth discoloration [17]. Response to trimethoprim–sulfamethoxazole has been reported in CBDC [18] but has also been reported as a cause, as mentioned. The combination of dapsone and nicotinamide in a patient with disease that that was previously refractory to dapsone and corticosteroid therapy has been reported [19], and resection of a diseased rectal stump in the setting of ulcerative colitis led to improvement after prednisolone, cyclosporine, and thalidomide had failed [12]. Mycophenolate mofetil has also been reported to be successful in treating several adult patients [20, 21] and one pediatric patient [22]. Withdrawal of culprit medication in cases of drug-induced LABD or CBDC is sufficient. Lastly, intravenous immunoglobulin (IVIg) and immunoadsorption has been used successfully in adults with LABD [17], but rituximab seems to have less benefit in adult patients with IgA-dominant diseases and thus may be less useful in CBDC [23].

2.2 Dermatitis Herpetiformis

DH is an immunobullous cutaneous sign of celiac disease. Clinical manifestations are similar in children and adults, classically described as an intensely pruritic symmetric eruption favoring extensor surfaces, although this "classic" presentation may be in the minority [24]. Variants in children have also been described, with presentations ranging from chronic urticaria [25] to digital petechiae [26]. Direct immunofluorescence (DIF) most commonly demonstrates granular IgA deposition within dermal papillae in both children and adults, although a variety of DIF findings have been reported [27] and, rarely, DIF can be negative [28]. Adjunctive serologic testing can demonstrate IgA antibodies to tissue transglutaminase, epidermal transglutaminase, and endomysium (or immunoglobulin G [IgG] antibodies if IgA deficient) [29].

In a series of 76 patients with childhood DH, cases most frequently presented between the 2nd and 7th years of life, and no cases presented earlier than 10 months of age [30]. Less than 40% had associated diarrheal symptoms, but most, if not all, gastrointestinal biopsies were abnormal [24, 30]. Frequency of presentation in childhood is mixed, with one series finding that 27% of 159 Italian patients presented before the age of 10 years [24]. In contrast, only 3.8% of 476 Finnish patients with DH were diagnosed in childhood, despite their high prevalence of adult DH [31]. An association between DH and autoimmune conditions, such as type 1 diabetes mellitus and thyroid disorders, is established in adult patients [32, 33]. However, in the Finnish study [31], none of the children with DH had associated autoimmune conditions, but they did have a familial history of celiac disease and DH [31].

Management is similar for children and adults. Ideally, treatment consists of a gluten-free diet, but resolution of cutaneous symptoms can take 1–6 months [30]. Thus, if symptoms persist despite starting a gluten-free diet, or if a gluten-free diet cannot be adhered to, dapsone is the treatment of choice [34]. Dapsone 2 mg/kg/day or 4 mg/kg weekly in pediatric patients is approximately equivalent to a dose of 100 mg daily in adults [34]. Of note, intestinal symptoms do not respond to dapsone or reduce the risk of DH-related complications such as intestinal lymphoma. Additional treatments have been reported in adult patients, including alternate sulfonamides, cyclosporine, colchicine, heparin, tetracycline, nicotinamide [29], and rituximab [35], but these have not been studied in children.

2.3 Pemphigus Vulgaris

Pemphigus vulgaris (PV) is an immunobullous mucocutaneous eruption with flaccid blisters and erosions most commonly caused by autoantibodies to desmoglein (Dsg)

Table 1 Summary of reported treatments in varying bullous diseases

Condition	First line (when known)	Alternatives reported in children	Alternatives reported in adults, not yet listed
Linear IgA bullous dermatosis	Dapsone 0.5 mg/kg/day, increased until symptom control (usually 2 mg/kg/day)	Sulfapyridine (not available in USA), corticosteroids, colchicine if G6PD deficiency; antibiotics (erythromycin, dicloxacillin, oxacillin), TMP-SMX, dapsone ± nicotinamide, mycophenolate mofetil, resection of diseased rectal stump in setting of ulcerative colitis, withdrawal of culprit medication if drug induced	IVIg, immunoadsorption, rituximab
Dermatitis herpetiformis	Gluten-free diet, dapsone 2 mg/kg/day or 4 mg/kg weekly		Alternate sulfonamides, cyclosporine, colchicine, heparin, tetracycline, nicotinamide, rituximab
Pemphigus vulgaris	Systemic corticosteroids 1.0–1.5 mg/kg/day with adjuvant	Adjuvants: azathioprine, dapsone, cyclophosphamide, plasmapheresis, IVIg, rituximab	
Pemphigus foliaceus	Systemic corticosteroids with adjuvant	Adjuvants: dapsone most commonly, erythromycin, chloroquine, azathioprine, sulfapyridine, methotrexate, corticotropin, mycophenolate mofetil, rituximab	
Paraneoplastic pemphigus	Removal of tumor when present	Adjuvants: corticosteroids, azathioprine, methotrexate, cyclosporine, cyclophosphamide, IVIg, rituximab, tocilizumab, plasma exchange, lung transplantation, IVIg	
Bullous pemphigoid	Systemic corticosteroids ± dapsone	Cyclosporine, erythromycin, doxycycline and niacinamide, azathioprine, mycophenolate mofetil, IVIg, plasma exchange, extracorporeal photochemotherapy, removal of renal allograft, rituximab	
Mucous membrane pemphigoid	Mild: topical steroids ± dapsone. Severe: systemic therapy, possibly surgical intervention	Prednisolone, dapsone, azathioprine	Erythromycin, cyclophosphamide, IVIg, rituximab
Epidermolysis bullosa acquisita	Systemic corticosteroids ± dapsone	Mycophenolate, cyclosporine, azathioprine	
Epidermolysis bullosa	Supportive therapy	Epidermolysis bullosa pruriginosa: thalidomide and cyclosporine; isotretinoin for chemoprevention of SCC	

G6PD glucose-6-phosphate dehydrogenase, *IgA* immunoglobulin A, *IVIg* intravenous immunoglobulin, *SCC* squamous cell carcinoma, *TMP-SMX* trimethoprim–sulfamethoxazole

1 and 3. DIF demonstrates intercellular IgG deposition in a "chicken wire" pattern. It is rare in children, with different features found in childhood (aged < 12 years) and juvenile (aged 13–18 years) cases compared with adult PV. Neonatal and stillborn cases have also been reported and are thought to be the result of transfer of maternal antibodies across the placenta [16, 36]. Other diseases in the pemphigus family have been reported in pediatric patients, including pemphigus herpetiformis [37, 38], IgA pemphigus [39, 40], pemphigus vegetans [41, 42], and gingival hypertrophy in association with antibodies against desmocollin 3 [43].

In a review of patients with childhood PV, mean age of onset was 8.3 years [44]. Compared with adult PV, but similar to juvenile PV, as follows, involvement of the genital and ocular mucosa was greater. Mean duration of therapy was 4.5 years, and prednisone was the most common therapy in nearly 80% of cases. Adjuvant steroid-sparing therapy was used in 36% of children. Mortality was lower than with adult and juvenile PV, but 67% of children developed adverse effects from systemic corticosteroids, most commonly cushingoid features, infections, and growth retardation, highlighting children's increased susceptibility to adverse effects [44].

A review of patients with juvenile PV reported that presentation was similar to that of adult PV but also had greater involvement of non-oral and ocular mucosa, as in childhood PV [45]. The mean age of onset was 14.9 years, and the majority was relatively clear of disease within 2 years (although it was not always known whether patients were receiving systemic therapy when the case was reported). Corticosteroids were most frequently used in treatment, often with a variety of adjuvant steroid-sparing therapy. Mortality was again lower than that in adult patients, but nearly 20% of children developed adverse effects, usually from corticosteroids [45]. Immunologic findings and diagnosis are the same in adult, childhood, and juvenile cases.

In neonatal cases, maternal disease is nearly always present. In a systematic review of 51 cases of neonatal AIBDs, 34 of which were pemphigus (31 PV and three PF), all but one mother had maternal disease. In this series, four deaths were reported (three premature stillbirths and one neonate at 10 days); all were from PV in the setting of active maternal disease requiring treatment although, in general, the authors did not find that maternal pemphigus activity corelated with neonatal pemphigus activity [16].

Recommendations for treatment of pemphigus is limited by the lack of data in the literature. Most commonly, systemic corticosteroids are used with adjuvants of azathioprine, dapsone, mycophenolate mofetil, cyclophosphamide, plasmapheresis, IVIg, and rituximab [45]. Given the high incidence of steroid-related adverse events in juvenile and childhood cases, efforts should be made to decrease the use of corticosteroids. The combination of mycophenolate mofetil and prednisone has produced durable remission in pediatric patients, leading to an ability to discontinue prednisone [46]; in adults, mycophenolate mofetil and azathioprine had similar efficacy and steroid-sparing effects [47]. IVIg has also been used in treatment of juvenile pemphigus, without the need for initial systemic corticosteroids and with a low side-effect profile [48]. Given the evidence for the use of rituximab as a first-line treatment for PV in adults [49], its use may also be considered in pediatric patients, but more studies are needed. In pediatric patients with PV who have been treated with rituximab, both fixed-dose and body-weight dosing have been used successfully, but the optimal regimen has not yet been defined [50, 51]. Overall, it is well-tolerated, with infusion reactions and infections reported as side effects [50, 51]; one death from sepsis was reported [52].

2.4 Pemphigus Foliaceus

PF is an immunobullous cutaneous eruption without mucus membrane involvement, usually a result of antibodies to Dsg1. DIF produces patterns similar to those of PV, albeit usually more superficial. Fogo selvagem, the endemic form of PF originally described in Brazil, can be quite common in children, with epidemiologic studies reporting incidences of 10–26% of cases occurring before the age of 14 years [53]. However, non-endemic PF in children is very rare. Clinical presentation in children and adults is similar, with superficial blisters and crusted erosions on the skin in a seborrheic distribution, although an unusual pattern of "arcuate, circinate, or polycyclic lesions" has been observed in cases of childhood PF [54]. Erythrodermic presentation [55], exfoliative presentation [56], and associated nonscarring alopecia have also been described [57]. Neonatal PF appears to be underrepresented in the neonatal population, which may be a result of Dsg3 overexpression in neonatal epidermis [16]. Immunologic findings and diagnosis across all age groups are the same; childhood PF has been described in association with antibodies against desmocollins [58].

In children with non-endemic PF, the mean age of presentation is 7.7 years. Sunlight exposure, drugs, infections, and Grave's disease have been reported in association with childhood PF, similar to in adult patients [54, 59]. A single association with neuromyelitis optica has been described in a pediatric patient but not in adults [60]. Prognosis for childhood PF may be better than that for childhood PV, with one review reporting that 88% of children were clear of PF, either off therapy or on low-dose maintenance therapy, within 1 year, but long-term follow-up is lacking [54]. One death from childhood PF has been reported, but it was in a patient treated in the 1950s who was not given steroids [61].

Recommendations for treatment are limited by the lack of data in the literature. To date, most treatment regimens for

childhood PF consist of systemic corticosteroids, with dapsone as the most common adjuvant therapy [54]. Additional treatments that have been reported include erythromycin, chloroquine, azathioprine, sulfapyridine, methotrexate, and corticotropin [54]. More recently, mycophenolate mofetil [62] and rituximab have also been used successfully [51, 55, 63, 64]. As with the treatment of childhood PV, dosing questions and side-effect concerns remain [61].

2.5 Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) occurs in the presence of an underlying malignancy, most commonly non-Hodgkin's lymphoma in adults and Castleman's disease in children. In contrast with other immunobullous diseases in children, which often portend a better prognosis or lower mortality than in adults, childhood PNP continues to demonstrate very high mortality rates, which may be due to the high rates of pulmonary involvement leading to bronchiolitis obliterans (BO) [65, 66]. The most frequent clinical manifestation is severe stomatitis in both children and adults. However, unlike adult cases, cutaneous lesions in childhood PNP are more likely to be lichenoid than blistering in nature [65].

The average age at presentation of childhood PNP is 13–14 years, with the disease occurring most often at 16 years [66]. Histopathologic and immunologic findings can be quite varied but are similar in children and adults. Histopathology often demonstrates a combination of lichenoid dermatitis with intraepithelial acantholysis. DIF similarly exhibits a mixed pattern, showing both intercellular IgG and C3 deposition as well as linear deposition along the BMZ. The major autoantibodies in PNP are against plakins and desmogleins [65]; additional autoantibodies to desmocollin and alpha-2-macroglobulin-like protein 1 have also been described [67]. Newer evidence from two predominantly adult populations highlights potential autoantibody–clinical phenotype correlations, with Dsg3 [67] and epiplakin autoantibodies [68] associated with the development of BO. Similar correlations have not yet been studied in children.

Treatment for PNP is surgical resection of the underlying tumor when present, which generally seems to improve mucocutaneous lesions, although it may take months. Unfortunately, removal of tumor does not seem to improve pulmonary involvement, and BO, leading to death, has been reported to develop even after resection of Castleman's disease [69]. The use of adjuvant immunosuppressants has also been reported, including corticosteroids, azathioprine, methotrexate, cyclosporine, cyclophosphamide, IVIg, rituximab, tocilizumab, and plasma exchange, but treatment is often unsatisfactory, particularly with pulmonary involvement [66]. Lung transplantation may improve survival, and IVIg may aid in bridging to lung transplantation [66].

2.6 Bullous Pemphigoid

BP is a subepidermal immunobullous disorder, characterized by autoantibodies to BP antigens 180 and 230 as well as by DIF demonstrating linear IgG and C3 at the BMZ in an n-serrated pattern. Salt-split skin, in which specimens are treated with 1 M NaCl to induce cleavage in the lamina lucida and thus aid in more specific localization of autoantibodies, will demonstrate epidermal staining. Histopathologic and immunofluorescence findings are similar in adults and children.

The classic presentation of intensely pruritic urticarial plaques and tense bullae in an elderly male is well-known, but pediatric cases have also been reported and presentation varies. One review of 78 cases found two peaks of onset in childhood, with 53% of cases occurring in the first year of life at a median age of 4 months and a second peak at a median age of 8 years in 47% of cases [70]. In infantile BP, acral involvement is very common. Childhood BP has a higher frequency of vulvar involvement. An additional subset of BP localized to the genital region was also identified that occurred almost exclusively in girls and can mimic sexual abuse [70]. Neonatal cases have been described, usually in the presence of maternal pemphigoid gestationis [16]. Additional variants have been described, including pemphigoid nodularis [71–73], pemphigoid vegetans [74], dyshidrosiform pemphigoid [75], anti-p200 pemphigoid [76], BP in association with chronic renal allograft rejection [77], and BP following vaccination [78] (Fig. 2). Interestingly, one of the cases of pemphigoid nodularis occurred in the setting of IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome [72], which is a condition caused by mutations in the *FOXP3* gene and leads to dysfunctional regulatory T cells (Tregs). The association between pemphigoid diseases and IPEX syndrome is notable, as recent studies have demonstrated that dysfunction of Tregs leads to production of BP autoantibodies [79, 80].

In general, treatment response was fast and prognosis good in childhood BP compared with adult BP [70, 81], with an average disease duration of 14 months (range 1.5 months to 5 years) in one series [81]. Treatment of choice is generally steroids with or without dapsone, although recommendations are limited to case reports and series. Additional treatments reported in the literature include cyclosporine [82], erythromycin, doxycycline plus niacinamide (in a patient aged > 8 years), and azathioprine [2]. Successful use of mycophenolate mofetil [83], IVIg [84], plasma exchange and extracorporeal photochemotherapy [85], removal of renal allograft in instances of chronic renal allograft rejection [77], and rituximab [86] has also been reported. Two deaths in association with rituximab for treatment of BP have been reported: one with a history of bone marrow transplant and graft-versus-host disease who also received

Fig. 2 Vaccine-induced bullous pemphigoid

daclizumab [87] and one who had congenital T cell lymphopenia [86]. Additional side effects reported included a non-infective secretory enteropathy, parainfluenza pneumonia, varicella zoster virus sepsis, and hypogammaglobulinemia in one patient [88].

2.7 Mucous Membrane (Cicatricial) Pemphigoid

Mucous membrane (cicatricial) pemphigoid (MMP) is a group of immunobullous subepidermal conditions, all of which are manifested by mucosal involvement, often with scarring. It is quite rare in children but presents similarly to that in adults, with heterogenous antigen targets. DIF findings are similar to those for BP, although in cases of anti-laminin 332 MMP, salt-split skin will result in dermal staining. Indirect IF is frequently negative. In a review of 18 cases in the literature, the average age of onset was 10.3 years (range 20 months to 18 years) [89]. Desquamative gingivitis was the first presentation of oral MMP, and the oral cavity was the most common site of involvement. Ocular involvement was also reported, at times developing several years after disease onset [89]. Additional studies have since described cases of pediatric anti-laminin 332 MMP [90, 91]. In adults, this subtype of MMP is associated with

an increased risk of cancer, but the risk of cancer in children with MMP is unknown.

Clinical manifestations of childhood MMP are variable, at times with a favorable prognosis requiring only topical steroids and dapsone; however, it can also be severe and require systemic immunosuppressants and surgical intervention [89]. Cases have also utilized prednisolone, dapsone, azathioprine, and erythromycin. Ocular disease carries a risk of blindness and deserves aggressive therapy. Cyclophosphamide and prednisone are recommended in adults, though this side-effect profile may be less favorable in children [89]. IVIg [92] and rituximab [93], which have been used in adults with MMP, are not well-studied in children but could be considered as steroid-sparing agents.

2.8 Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is a very rare immunobullous subepidermal condition. The two main types are the classic, non-inflammatory mechanobullous variant and the inflammatory type. The non-inflammatory variant is more common in adults, presenting as acral blisters with frequent scarring and milia, whereas the inflammatory type is more common in children [94], particularly those aged < 5 years [95], and may mimic BP or other inflammatory bullous disorders. Mucosal involvement, especially of the oral cavity, is more commonly reported in childhood EBA [94]. One case of self-limited neonatal EBA has been reported as a result of transplacental maternal antibody transfer [96]. Histopathologic findings vary on subtype, as above, but immunologic findings are similar in adults and children. DIF demonstrates linear immunoglobulin deposition (most commonly IgG) along the BMZ, with a u-serrated pattern. Salt-split skin will demonstrate dermal staining. While the pathogenic autoantibody in EBA is to type VII collagen, and the noncollagenous (NC) 1 domain of type VII collagen is most frequently targeted in adult patients, reactivity to the NC2 domain and triple helical domain have been reported in childhood EBA [94].

Age of onset in the pediatric population has been reported to occur between 2 weeks and 17 years [97]. Like in adults, conditions associated with EBA have been reported, including Crohn's disease and ulcerative colitis [97]. Additional associations described in childhood EBA include IPEX syndrome, celiac disease, PV and malignant lymphoma, penicillamine, squaric acid dibutyl ester immunotherapy for alopecia areata, and various autoantibodies [97].

Treatment response and prognosis is typically much better in children than in adults, with most childhood patients responding to dapsone and prednisone [94]. Mycophenolate mofetil has also been used successfully in a patient who had persistent symptoms on prednisolone and dapsone [98]. Occasionally, the disease can be more severe, particularly in

patients with IgA autoantibodies and ocular involvement, which has led to the use of cyclosporine [99, 100] and azathioprine [100].

3 Inherited Bullous Conditions

3.1 Epidermolysis Bullosa

In contrast with the discussed bullous conditions, EB is not an autoimmune bullous disease but rather a group of inherited bullous disease caused by mutations in key proteins in the BMZ. The four major types of EB are EB simplex (EBS) (Fig. 3), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome [101]. Clinically, EB almost always presents at birth or in early childhood, with the JEB late-onset subtype still presenting between the ages of 5–8 years [102]. Diagnosis can be made using a combination of immunofluorescence antigen mapping, transmission electron microscopy, and genetic mutational analysis [101].

Clinical presentation is similar in children and adults, with cutaneous and systemic features varying according to EB subtype. Some complications may take years to develop and are thus more common in older populations. Associated malnutrition, osteopenia, iron deficiency, and growth delay are well-documented in severe EB subtypes. Mild subtypes may only exhibit blistering on the hands and feet during certain times of the year. The risk of squamous cell carcinoma (SCC) is increased in patients with recessive DEB (RDEB), generalized severe subtype (previously RDEB, Hallopeau–Siemens), that begins in adolescence but increases throughout adulthood, starting as a 7.5% risk of at least one SCC by age 20 years and reaching a risk of 90%

Fig. 3 Generalized epidermolysis bullosa simplex (due to *exophilin 5* mutation)

by 55 years [103]. The risk of melanoma is also increased in patients with RDEB, generalized severe, and EBS, generalized severe (previously EBS Dowling–Meara) [103]. Other features may improve or change over time, such as in the case of Kinder syndrome and generalized EBS, where blistering can decrease over time [101].

No cure exists for EB, but many new therapies are on the horizon [104]. Treatment options are similar between children and adults, with supportive treatment focused on wound care and infection prevention for cutaneous signs and multidisciplinary care with appropriate specialists for systemic signs. Systemic therapy with anti-collagenase, anti-inflammatory, or anti-fibrotic effects, such as phenytoin, tetracyclines, cyclosporine, and etanercept, have been trialed with occasional success, sometimes before the understanding of the pathogenesis of EB [104]. Specific EB subtypes may benefit from certain treatments, such as thalidomide [105] and cyclosporine [106–108], which have been used in the treatment of epidermolysis bullosa pruriginosa. Additionally, isotretinoin was, overall, well-tolerated in a phase I trial in RDEB and may prove beneficial in chemoprevention of SCC, although it can lead to increased skin fragility [109]. Cell therapies, including allogeneic fibroblasts, mesenchymal stromal cells, bone marrow transplantation, grafting of revertant skin and keratinocytes, gene therapy, and protein therapy, are also being studied [104].

4 Special Considerations When Treating Pediatric Patients

When treating pediatric patients, the usual side effects of any medications should be considered. Additional considerations should include how certain medications may affect growing and developing children, such as the growth delay seen with systemic corticosteroids and the permanent tooth discoloration seen with tetracyclines (Table 2). The effect of rituximab on the immune system, especially as it pertains to protection against vaccine-preventable diseases, is also a concern. Evidence in the pediatric AIBD population is limited, but literature does support that the effects of rituximab on B and T cells likely has some impact on vaccine response [110]. Expert opinion recommends completing vaccinations before starting rituximab when possible, otherwise optimal vaccine response is expected to occur at least 6 months after the last dose of rituximab [110].

5 Conclusions

Bullous diseases are uncommon in children. Infection should always be initially considered and excluded. Immunologic diagnosis and treatment are often similar to that for adults,

Table 2 Select medications used in the treatment of childhood bullous diseases with special considerations for pediatric populations

Medication	Considerations for pediatric populations
Corticosteroids	Growth impairment, cataract formation
Rituximab	Possible effects on vaccination response; experts recommend completing vaccines before starting rituximab when possible
Tetracyclines	Permanent tooth discoloration; contraindicated in children aged < 8 years

but clinical presentations may vary. Prognosis and response to treatment is generally better in children than in adults, except in the case of PNP. When treating pediatric populations, special considerations are required.

Compliance with Ethical Standards

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