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Bullous diseases: Kids are not just little people☆

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Abstract Bullous diseases may be rare; however, this does not preclude the clinician from being familiar with their manifestations and treatment. After ruling out infection, genetically inherited blistering diseases are more likely to be the cause of blistering or erosions in the neonatal period, whereas immunobullous diseases are more common in adults. Published literature on immunobullous disorders reflects information gleaned from case reports and open-label case series; prospective studies and evidence-based treatments are limited. Although there may be overlapping clinical features, significant clinical differences exist between adults and children. Evidence-based treatment guidelines are limited, and information from the adult literature cannot be readily generalized to the pediatric population. This paper reviews the approach to blistering conditions and the differences among bullous pemphigoid, linear immunoglobulin A disease, dermatitis herpetiformis, pemphigus foliaceus, pemphigus vulgaris, and paraneoplastic pemphigus in adult versus pediatric patients.

What is the approach to the workup of blistering disorders in children versus adults?

When a neonate presents with blisters, the differential diagnosis is extremely broad, ranging from infectious diseases such as herpes simplex virus (HSV) to genetically inherited blistering disorders such as epidermolysis bullosa (EB) (Table 1). Infectious causes are the most immediate concern, and so the initial workup should include testing for viral, bacterial, or fungal infections. Certain patterns of vesicles may yield a clue to the diagnosis (eg, linear blistering in incontinentia pigmenti),[1,2] but when HSV is suspected, a low threshold for infection must be maintained because the presence of incontinentia pigmenti or other genodermatosis does not rule out the co-existence of an infection.[3] Several reports have also described HSV as initially resembling the lesions of blistering disorders such as EB; therefore, it is important to perform prompt laboratory testing to rule out infection early on, because missing an HSV infection could have fatal consequences.[4–6] Treatment for an infection can be instituted empirically while awaiting culture results; treatment should be continued when the clinical suspicion is high despite negative initial culture results. (See Figs. 1– 4.)

If an inherited blistering disease such as EB is suspected, a skin biopsy of a freshly induced blister should be performed for direct immunofluorescence (DIF) testing and sent to a qualified laboratory. The panel of proteins for which tests can be run includes keratin 5 and 14, collagen VII, collagen XVII, laminin 5, alpha 6 beta 4 integrin, and plectin.

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Table 1 Different approaches to blistering disorders in pediatric vs adult patients

	Children	Adults
Most common causes	Infections: *Viral (HSV), bacterial, and fungal*	Autoimmune bullous disorders: *Bullous pemphigoid most common*
Other common causes	Hereditary blistering disorders: *Epidermolysis bullosa (EB)*	Infections: *Viral (HSV), bacterial, and fungal*
	Autoimmune bullous disease: *LABD most common*	Hereditary blistering disorders: *Epidermolysis bullosa*
Approaches to workup	Wound culture to rule out viral, bacterial, and fungal infection	Wound culture to rule out viral, bacterial, and fungal infection
	Newborn: If suspect EB, skin biopsy of freshly induced blister for DIF keratin 5 and 14, collagen VII and XVII, laminin 5, alpha 6 beta 4 integrin, and plectin	Skin biopsy for H&E and DIF if suspicious for autoimmune bullous disorders
	Acquired in infancy or childhood: Skin biopsy for H&E and DIF if suspicious for autoimmune bullous disorders	ELISA or IIF for circulating autoantigens
	ELISA or IIF for circulating autoantigens	

DIF, Direct immunofluorescence; *H&E,* hematoxylin-eosin staining; *HSV,* herpes simplex virus; *IIF,* indirect immunofluorescence; *LABD,* linear immunoglobulin A bullous dermatosis.

Acquired immunobullous diseases in newborns are exceedingly rare and usually occur in the setting of transplacental passage of maternal autoantibodies (see next section). The diagnosis is generally made in the mother and serum antibodies can be analyzed in the neonate. If an acquired immunobullous disease is suspected in an older child or an adult, two punch biopsy specimens should be obtained, one lesional for hematoxylin-eosin staining (H&E) and one perilesional (0.5-1 cm away from the edge of a lesion) for DIF. The immunofluorescence staining pattern can be very useful to making the diagnosis. Indirect immunofluorescent (IIF) testing has no role in the testing of neonates with genetically inherited blistering disorders but is important in establishing a diagnosis of an acquired or transplacentally transmitted autoimmune bullous disorder. IIF for immunoglobulin G (IgG) and IgG4 antibodies to desmogleins 1 and 3 should be checked if suspicious for pemphigus vulgaris (PV) and its variants, whereas IIF for BP 180 and BP 230 antibodies should be checked if considering a diagnosis of pemphigoid. IIF testing for antibodies to plakins can be checked when paraneoplastic pemphigus is suspected.

A rare situation unique to the newborn period is when blistering occurs after phototherapy for hyperbilirubinemia, which should prompt evaluation for rare diseases such as porphyria.[7,8]

How does pediatric bullous pemphigoid differ from the adult-onset variant?

Bullous pemphigoid (BP) is primarily seen in elderly populations and is a very rare condition in children, with fewer than 100 pediatric cases reported in the literature[9]

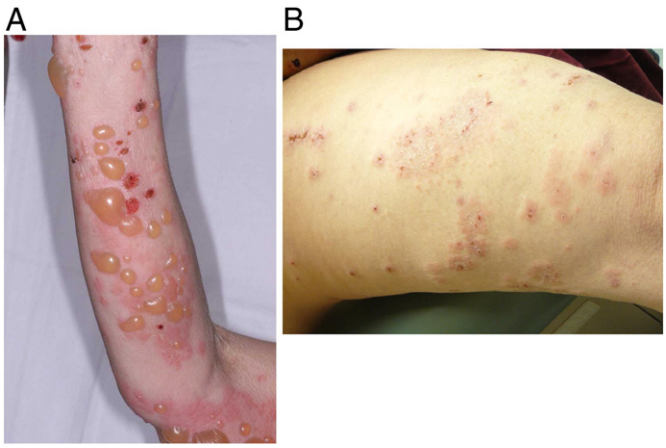

Fig. 1 Bullous pemphigoid in an adult patient. A, Tense bullae, erosions, and erythematous patches on the arm. B, Urticarial papules and plaques with excoriations.

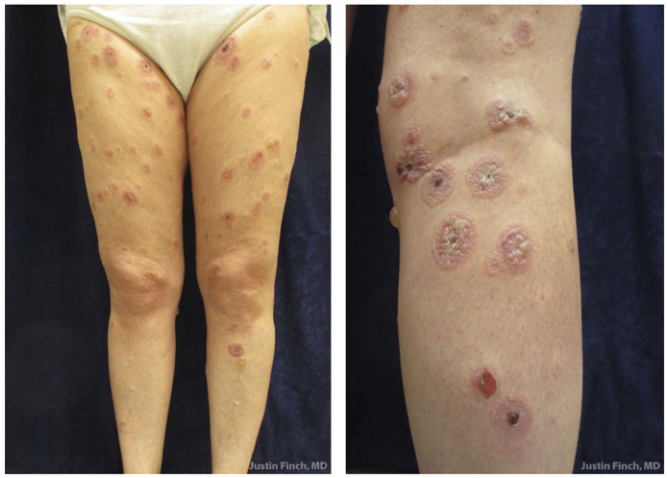

Fig. 2 Linear immunoglobulin A bullous dermatosis in an adult. Grouped or annular papules, vesicles, and bullae on thighs and legs. (Courtesy Justin Finch, MD.)

(Table 2). Clinically, BP is often pruritic, with urticarial wheals and plaques forming, then evolving into tense bullae. One major distinction between the pediatric subset and its adult counterpart is the clinical presentation. Pediatric BP has a female predominance, and three variants have been described: infantile, childhood, and localized vulvar disease. Acral involvement (palms, soles, and head) is more common in infantile BP, whereas the childhood variant presents with more diffuse involvement and can involve the mucosa.[9,10] Oral ulcerations were present in three of six patients with childhood BP in one case series.[11] As in adults, lesions are often pruritic and nonscarring.[12]

Another difference between the adult and pediatric forms is the prognosis: Pediatric BP tends to have a favorable prognosis, with the majority of patients achieving remission in weeks to months[9,11]; adult-onset disease is more chronic, with significant morbidity and mortality.[13,14] Potent and ultrapotent topical steroids can be used in localized disease.[15]

Pediatric BP, like adult-onset BP, shows eosinophils, but also commonly shows a mixed infiltrate with neutrophils,[11] which may be the reason dapsone (which targets neutrophils) has been reported to have some benefit in pediatric as well as adult case reports.[12,16,17] Antibiotics such as erythromycin (with or without the addition of niacinamide, a B-group vitamin with anti-inflammatory properties) have been beneficial in some children.[18–20] Of note, although tetracycline antibiotics have been used with some success in adult BP patients,[21,22] this class of antibiotic is contraindicated in children younger than age 8 years due to dental effects. Other adjunctive therapies that have been used for severe cases of BP include intravenous immunoglobulin (IVIG), cyclosporine, azathioprine, and mycophenolate mofetil.[23–28] In one case report in which the patient failed treatment with corticosteroids, IVIG, dapsone, and cyclosporine, rituximab was utilized with successful remission of disease.[29] Of note, mortality in BP is often attributed to complications of systemic treatment.

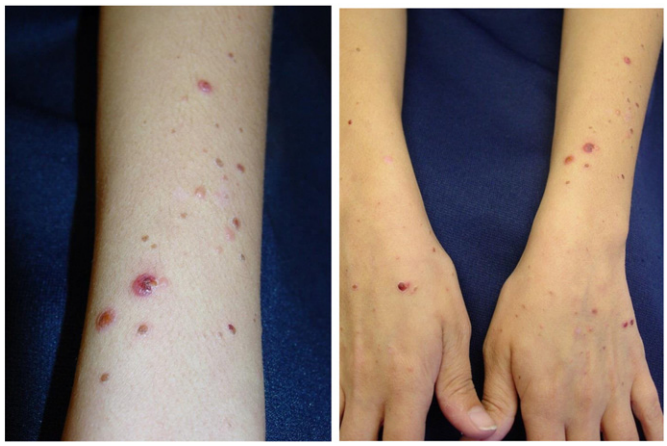

Fig. 3 Linear immunoglobulin A bullous dermatosis of childhood. Clear or hemorrhagic bullae on a normal or erythematous base involving arms and dorsal hands of a 10-year-old girl. (Courtesy Judith V. Williams, MD.)

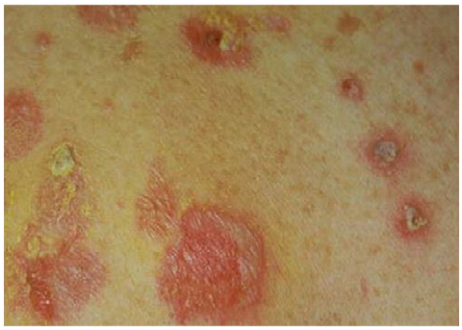

Fig. 4 Pemphigus in an adult. Pemphigus vulgaris with flaccid blisters, erosions, and crusting lesions present on the back.

How does pediatric epidermolysis bullosa acquisita differ from the adult variant?

Childhood epidermolysis bullosa acquisita (EBA) is also a very rare immunobullous condition, with fewer than 50 cases reported in the literature (Table 3). Two subtypes have been described: A noninflammatory scarring process with development of milia similar to dystrophic EB, and an inflammatory version that is clinically indistinguishable from BP and other immunobullous diseases.[12,30,31] The mechanobullous type tends to be more common in adults and older children, whereas the inflammatory subtype is more commonly seen in children younger than 5 years.[31,32] Blisters tend to be present on extensor surfaces of extremities at sites of trauma and can be hemorrhagic or filled with serous fluid.[30] Mucosal involvement is more common in the childhood variant than the adult form, with oral and ocular lesions most common.[31–34] Nail dystrophy and alopecia may also be present, as in the inherited form. One case reported an association between childhood EBA and dental enamel alterations, a finding that is common in the inherited form of EB.[35] The clinical findings result from the deposition of antibodies against collagen 7, which composes the anchoring fibrils of the basement membrane.[36] The antibodies are most commonly IgG, but a small subset of patients express IgA antibodies, leading to more severe mucosal involvement.[32,37] In the IgA subtype of pediatric EBA, cases of subsequent blindness have been described.[38,39]

Adults with classic EBA tend to have autoantibodies to the NC1 domain of collagen 7; however, in the pediatric inflammatory phenotype, Mayuzumi et al. reported that the antigen was more often in the NC2 or triple helical domain.[31] Prognosis of childhood EBA is better than adult-onset disease, with remission achieved with systemic corticosteroids and dapsone in the majority of cases.[31,40,41] Adjunctive treatments such as mycophenolate mofetil,[42] IVIG,[35] and colchicine[39] have been used in resistant pediatric cases with reported success. Rituximab has also been reported to be successfully used in adult cases that have failed other therapeutic options.[43,44]

Table 2 Bullous pemphigoid (BP) in pediatric vs adult patients

	Children	Adults
Epidemiology	Rare: <100 case reports Female predominance Reported in infants and children	Most common: 12–14 cases/million/yr F = M Most patients >60 years old
Risk factors	Neonates: should consider passage of maternal autoantibodies	Neurologic disorders: stroke, Parkinson's, bipolar disorder Consider medications: furosemide, spironolactone, glyptin, metformin
Workup	Skin biopsy for H&E and DIF ELISA for BP180 and BP230	Skin biopsy for H&E and DIF ELISA for BP180 and BP230
Clinical features	Three clinical variants: *Infantile*—acral involvement common *Childhood*—more diffuse ± oral ulcers *Localized genital BP*—rare	Blister and nonblister variants: *Classic blisters and vesicles* (most common presentation) *Urticarial, eczematous, prurigo* *Mild and mucosal involvement*
Prognosis	Favorable; most achieve remission in weeks to months	More chronic with significant morbidity and mortality. Mortality often attributed to complications of systemic treatment.
Treatment[a]	First line: Topical/systemic corticosteroids Antibiotics: Erythromycin Dapsone or sulfapyridine Case reports of steroid-sparing agents in refractory cases Mortality often attributed to complications of systemic treatment	First line: Topical/systemic corticosteroids Antibiotics: Tetracycline ± nicotinamide Case reports of steroid-sparing agents in refractory cases Mortality often attributed to complications of systemic treatment

DIF, Direct immunofluorescence; *F,* female; *H&E,* hematoxylin-eosin staining; *M,* male.
[a] Off-label.

How does linear IgA bullous dermatosis differ in children versus adults?

Chronic bullous dermatosis of childhood, now called linear IgA bullous dermatosis (LABD) given its immunohistochemical similarities to the so-named adult condition, is another immunobullous condition that presents in childhood (Table 4). Although still very rare, LABD is the most common of the immunobullous diseases in childhood.[45] Before the discovery of characteristic immunofluorescence findings, this condition was included with dermatitis herpetiformis in the literature. LABD is characterized by the deposition of IgA along the basement membrane zone, which causes a subepidermal blister. One distinction between children and adults is the clinical presentation. In children, the blisters appear in an annular configuration in a "cluster of jewels" or "string of pearls" pattern, with new lesions appearing at the periphery of older lesions. The lesions appear on the abdomen, groin, and thighs, with a predilection for the anogenital skin.[46] In adults, the lesions appear on the face, extensor surfaces, buttocks, and trunk.[46] In the pediatric population the incidence is highest in children aged 4 to 5 years, and only rarely has LABD been noted in neonates.[47–51] LABD can be drug induced or idiopathic. Mucosal lesions may occur in up to 70% of adult patients with linear IgA disease, ranging from asymptomatic ulcers to severe oral and conjunctival disease typical of that seen in cicatricial pemphigoid.[52] Mucous membranes can be involved in up to 80% of affected children[53–56] and can also be severe.[49] Two reports describe infants with severe upper aerodigestive disease that resolved with treatment using prednisone and dapsone[47,53]; one of the two received IVIG as well.[53] One patient developed severe ocular involvement with subsequent blindness in one eye.[47] Diffuse airway involvement may require prolonged treatment with corticosteroids, and patients may have relapses.[53] Very rarely, IgA nephropathy can develop, and these patients should be screened accordingly with urinalyses to detect hematuria and proteinuria, which may be asymptomatic.[57] Compared with adult disease, childhood linear IgA bullous disease has a better prognosis and tends to improve over time.[58] Standard of care is treatment with dapsone, but antibiotics, mycophenolate mofetil, corticosteroids, colchicine, and sulfapyridine have also been used with varying success.[20,59–61] Sulfapyridine, although also a sulfonamide antibiotic, only rarely cross-reacts and may be considered in dapsone-allergic patients; however, it is not readily available and, therefore, sulfasalazine is used as an alternative; it is metabolized to sulfapyridine after ingestion.[62] Drug-induced linear IgA, more common in adults than children,[63] and may respond to stopping the medication culprit, although some cases require systemic immunosuppression as well. Vancomycin is the most commonly and conclusively implicated culprit drug.

What are the differences between dermatitis herpetiformis in pediatric versus adult patients?

Dermatitis herpetiformis (DH) is classically described as presenting with exquisitely pruritic papulovesicles on the elbows and other body sites (Table 5). The lesions are so pruritic that the intact vesicles are rarely visualized and eroded papules are present more often. Clinical manifestations in children may be similar to adults, but there have been reports of nonpruritic and other uncommon presentations in children. Lesions in pediatric patients have also been reported to mimic arthropod bite reactions, scabies, pityriasis lichenoides et varioliformis acuta, and chronic urticaria.[64,65] Purpuric palmar lesions have been reported in adults, and an atypical presentation of palmar-only lesions has been reported in a child.[66] Ataxia and neurologic symptoms have been reported in both adults and children.[67] Interestingly, DH was first found to be associated with gluten hypersensitivity when a Dutch pediatrician, Dr. Willem Dicke, found that his patients with celiac disease improved during World War II when bread was in short supply. Symptoms returned when rations were back to normal. Treatment for adults and children is similar. A lifelong gluten-free diet is recommended. The gastrointestinal findings respond quickly to a gluten-free diet, although the skin manifestations can take up to a year to improve. Mild cases may be treated with topical steroids while awaiting improvement with gluten avoidance; however, dapsone is the treatment of choice for skin disease in both children and adults after ruling out glucose-6-phosphate dehydrogenase (G6PD) deficiency. Treatment must be started slowly and closely monitored with frequent blood testing because hemolysis is expected even without G6PD deficiency and compensatory reticulocytosis will need to occur. The skin tends to responds quickly to treatment with dapsone, whereas the gut does not respond to this therapy. A gluten-free diet is essential not only because dapsone will not control the gastrointestinal manifestations of the condition but also because enteropathy-associated T-cell lymphoma has been reported in celiac disease patients with ongoing gluten exposure.

What are the differences between pemphigus foliaceus in children versus adults?

The endemic form of pemphigus foliaceus (PF), also known as fogo selvagem, mainly affects children and young adults in rural Brazil (Table 6). This endemic form occurs after the bite of the black fly, *Simulium nigrimanum*. Other arthropod vectors such as the sand fly may also be implicated.[67] The sporadic form of PF is a disease of middle-aged to elderly patients and is rare in children. When the sporadic form occurs in children, it may present with a dramatic pattern of crusted plaques and erosions with an

Table 3 Epidermolysis bullosa acquisita in pediatric vs adult patients

	Children	Adults
Epidemiology	Rare: < 50 cases reported	Rare, sporadic
Risk factors	Not known	F = M Median age onset: 44 years Inflammatory bowel disease Anecdotal reports of other autoimmune diseases
Pathogenesis	IgG (rarely IgA) Abs to collagen 7: NC2 or triple helical domain NC1 domain	IgG (rarely IgA) Abs to collagen 7: NC1 domain
Workup	Skin biopsy for H&E and DIF Salt-split DIF IIF or/and ELISA to NC-1 Western blot	Skin biopsy for H&E and DIF Salt-split DIF IIF or/and ELISA to NC-1 Western blot
Clinical features	Most common: Inflammatory subtype and oral involvement younger than age 5 years (nonscarring) Less common: Classic mechanobullous type	Most common: Classic mechanobullous type Bullous pemphigoid–like Other less common subtypes: Cicatricial pemphigoid–like Brunsting-Perry pemphigoid–like Linear IgA dermatosis–like
Prognosis	Favorable; most achieve remission with systemic meds	More chronic and refractory to treatment
Treatment [a]	First line: systemic corticosteroids + dapsone Case reports of other steroid-sparing agents	First line: systemic corticosteroids + dapsone + colchicine Case reports of other steroid-sparing agents

DIF, Direct immunofluorescence; *F,* female; *H&E,* hematoxylin-eosin staining; *IgA,* immunoglobulin A; *IgG,* immunoglobulin G; *IIF,* indirect immunofluorescence; *M,* male.

[a] Off-label.

Table 4 Linear IgA bullous dermatosis in pediatric vs adult patients

	Children	Adults
Epidemiology	Most common immunobullous disease in children Incidence highest at age 4–5 years	Rare, sporadic Onset after age 40 years
Disease associations	Not known	Drug-induced: Vancomycin, lithium, phenytoin, furosemide, sulfamethoxazole Inflammatory bowel disease Lymphoid or other malignancy
Pathogenesis	Linear IgA deposition at basement zone to multiple antigens: BP180, BP230, LAD285, laminin332	Linear IgA deposition at basement zone binding multiple antigens: BP180, BP230, LAD285, laminin332
Workup	Skin biopsy for H&E and DIF	Skin biopsy for H&E and DIF
Clinical features	Tense bullae "cluster of jewels" distribution Predilection for perineum and perioral region Mucous involvement up to 80%: Can be severe and scarring	Grouped or annular papules, vesicles, and bullae on extensor surfaces of elbows, knees and buttocks Mucosal involvement up to 70%: Can be severe and scarring Drug-induced can be EM or TEN-like
Prognosis	Favorable, spontaneous remission over time	Unpredictable Most have chronic disease with episodes of spontaneous remission
Treatment [a]	First line: Dapsone or sulfapyridine ± low-dose prednisolone Antibiotics: Dicloxacillin, erythromycin Case reports of steroid-sparing agents	First line: Dapsone or sulfapyridine ± low-dose prednisone Case reports of steroid sparing agents For drug-induced disease: Stop the inducing medications

DIF, Direct immunofluorescence; *EM,* erythema multiforme; *H&E,* hematoxylin-eosin staining; *IgA,* immunoglobulin A; *TEN,* toxic epidermal necrolysis.

[a] Off-label.

Table 5 Dermatitis herpetiformis in pediatric vs adult patients

	Children	Adults
Epidemiology	Infrequent in children F > M	Mean age of onset: fourth decade M/F: 2:1
Risk factors	HLA subtypes Family history Autoimmune disease, especially thyroid and IDDM	HLA subtypes Family history Autoimmune disease, especially thyroid and IDDM
Workup	Skin biopsy for H&E and DIF Tissue transglutaminase antibodies (tTG-IgA) ± antiendomysial antibodies (EMA) IgA level	Skin biopsy for H&E and DIF tTG-IgA ± EMA IgA level
Clinical features	Intensely pruritic vesicles, eroded papules on extensor surfaces, scalp Can resemble arthropod bites, scabies, PLEVA	Intensely pruritic vesicles, eroded papules on extensor surfaces, scalp
Prognosis	Favorable with lifelong gluten-free diet Skin responds quickly to treatment with dapsone Risk of enteropathy-associated T-cell lymphoma with ongoing gluten exposure	Favorable with lifelong gluten-free diet Skin responds quickly to treatment with dapsone Risk of enteropathy-associated T-cell lymphoma with ongoing gluten exposure
Treatment [a]	First line: Gluten avoidance Can try topical corticosteroids Dapsone Systemic steroids in severe cases	First line: Gluten avoidance Can try topical corticosteroids Dapsone (on-label) Systemic steroids in severe cases

DIF, Direct immunofluorescence; *F,* female; *H&E,* hematoxylin-eosin staining; *HLA,* human leukocyte antigen; *IgA,* immunoglobulin A; *IDDM,* insulin-dependent diabetes mellitus; *IIF,* indirect immunofluorescence; *M,* male; *PLEVA,* pityriasis lichenoides.

[a] Off-label.

"arcuate," "circinate," or "polycyclic" morphology on the face and scalp.[68] Most reported cases in children follow a relatively benign course and remit or resolve on minimal therapy within a year. In both adults and children, the prognosis of PF is overall more favorable than that of PV, although persistent and severe generalized cases do occur.[69]

What are the differences between PV in children versus adults?

PV can be severe and, before the advent of steroids, was associated with a high mortality rate in both children and adults (Table 7). In this condition, the first-line therapy is corticosteroids at any age. Because the condition often has a prolonged course with only rare spontaneous remission, numerous steroid-sparing agents have been reported for use in pemphigus with varying success.[70,71] One should note that the literature on treatment of pemphigus often includes the treatment of both patients with severe PF as well as PV. In the recent literature, rituximab, an anti-CD20 monoclonal antibody has been reported to be successful in a number of cases in adult as well as treatment-refractory pediatric patients. It was original labeled for use for lymphoma and is administered at a weight-adjusted dose given once a week for 4 weeks. It is also labeled for adult rheumatoid arthritis at a set dose of 1000 mg IV day 1, repeated on day 15. Both dosing protocols have been used in adults with pemphigus, whereas pediatric patients, unless they have reached an adult weight, have been treated with the scalable, weight-based dosing in the lymphoma protocol.[72]

Paraneoplastic pemphigus: What are the differences to be aware of in children versus adults?

Paraneoplastic pemphigus (PNP), also known as paraneoplastic autoimmune multiorgan syndrome (PAMS), is a blistering disorder that is associated with an underlying malignancy (see Table 6). The clinical features include intractable stomatitis, ocular involvement, bullous, erythema multiforme–like, or lichenoid lesions on the trunk and extremities, and involvement of the palms, soles, and nails. The severity of the skin lesions does not always parallel the severity of the underlying malignancy.[73] The stomatitis may be initially mistaken for HSV or Stevens-Johnson syndrome, and a paraneoplastic workup initially may not be considered, especially in pediatric patients.[74] The course can be complicated by bronchiolitis obliterans, respiratory failure, and death. Often, the cause of death is the underlying malignancy. In children, the most common cause is Castleman's disease (also known as angiofollicular hyperplasia, giant lymph node hyperplasia, localized nodal hyperplasia, benign giant lymphoma, or lymphoid hamartoma), which is a rare lymphoproliferative disorder that is disproportionately associated with PNP in children.[75–77] Some have proposed that the disease is a response to a viral infection such as Epstein-Barr virus or human herpes virus 8.[77] In adults, the

Table 6 Pemphigus in pediatric vs adult patients

	Children	Adults
Epidemiology	Pemphigus foliaceus (PF): Endemic PF (fogo selvagem) more common Pemphigus vulgaris (PV): Rare, can be seen in newborns (neonatal pemphigus)	Pemphigus foliaceus: Mostly sporadic, 0.5-1.0 cases/million/yr Pemphigus vulgaris: More common in Mediterranean descent Incidence varies, 1–10 cases/million/yr
Disease associations	Pemphigus foliaceus: Endemic PF: Black fly bite Neonatal pemphigus: Born to mothers with clinical pemphigus or circulating anti-Dsg 3 Abs	Drug induced: Penicillamine and captopril
Workup	Skin biopsy for H&E and DIF IIF and ELISA for Dsg1 and Dsg3	Skin biopsy for H&E and DIF IIF and ELISA for Dsg1 and Dsg3
Clinical features	Pemphigus foliaceus: Crusted plaques and erosions in polycyclic distribution on face and scalp Neonatal pemphigus: Vesicles and erosions trunk and extremities Mucosal involvement uncommon Self-resolving within weeks	Pemphigus foliaceus: Scaly and crusted erosion in seborrheic distribution, may progress to erythroderma Pemphigus vulgaris: Painful flaccid blister and erosions Mucosal involvement common, often first and only sign of disease
Prognosis	PF: Generally favorable; rare reports of severe cases PV: Potentially life threatening Neonatal pemphigus: Spontaneous remission	PF: Variable; severe cases similar to PV PV: Potentially life threatening
Treatment [a]	Neonatal pemphigus: Self-resolving within weeks Supportive care PV and severe PF: First line: Systemic corticosteroids Steroid-sparing therapies reported: Azathioprine, mycophenolate mofetil, IVIG, plasmapheresis, methotrexate, cyclophosphamide Biologics: Rituximab	PV and severe PF: First line: Systemic corticosteroids Steroid-sparing therapies reported: Azathioprine, mycophenolate mofetil, IVIG, plasmapheresis, methotrexate, cyclophosphamide Biologics: Rituximab

DIF, Direct immunofluorescence; *H&E,* hematoxylin-eosin staining; *IIF,* indirect immunofluorescence; *IVIG,* intravenous immunoglobulin.
[a] Off-label.

most common causes are non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease, sarcoma, and thymoma.[78] Although DIF is often negative, immunoblotting studies have revealed several target antigens, primarily in the plakin protein family.[30]

The development of PNP usually precedes the diagnosis of the underlying malignancy but can develop after treatment of the malignancy. In one case of a Castleman's disease recurrence, a 10-year-old girl developed PNP 5 years after the original diagnosis and treatment. She subsequently succumbed to bronchiolitis obliterans–induced respiratory failure.[79] One of the largest pediatric case series[76] reported 14 children with PNP. In this series, all of the patients suffered from stomatitis and all of them were found to have antibodies to plakins. They found that the majority (10/14) developed bronchiolitis obliterans pneumonia, and those with respiratory involvement had worse prognoses and higher mortality. Progression and death occurred despite treatment of the underlying malignancy or with immunosuppressive therapy for PNP. Unlike adults, they found that the skin findings in the pediatric patients tended to be more lichenoid and less blistering.

Treatment of PNP includes treatment of the malignancy and palliative immunosuppression, which can lead to remission of the blistering disease, but often in this ominous disease the ultimate prognosis remains poor.[73,76,80,81] Although no evidence-based treatment recommendations are available, there is a report suggesting that early recognition and removal of a Castleman's tumor as well as perioperative IVIG may mitigate the risk of subsequent bronchiolitis obliterans.[79]

What are special considerations in women of childbearing potential with autoimmune bullous diseases?

Transplacental antibody transfer or vertical transmission of pathogenic antibodies has been described in several

Table 7 Paraneoplastic pemphigus in pediatric vs adult patients

	Children	Adults
Underlying disease	*Castleman's disease* Giant lymph node hyperplasia Benign giant lymphoma Sarcoma	*Non-Hodgkin's lymphoma* Chronic lymphocytic leukemia Castleman's disease Sarcoma and thymoma
Clinical features	Intractable stomatitis Ocular involvement common Bullous or lichenoid lesions	Intractable stomatitis Polymorphous cutaneous eruption: Bullous, EM-like, lichenoid
Workup	Skin biopsy for H&E and DIF IIF and immunoblotting to desmogleins and desmoplakins Patients with no preexisting neoplasm: Imaging and workup for malignancies	Skin biopsy for H&E and DIF IIF and immunoblotting to desmogleins and desmoplakins Patients with no preexisting neoplasm: Imaging and workup for malignancies
Prognosis	Poor; respiratory failure due to bronchiolitis obliterans more common	Benign or encapsulated tumors: Fair prognosis relative to others Malignant neoplasms: Poor
Treatment [a]	Treatment of malignancy Palliative immunosuppression	Benign or encapsulated tumors: Tumor removal + immunosuppression after surgery (prednisone + rituximab) for 1–2 years Malignant neoplasms: Respond poorly to treatment with various immunosuppressant therapies Small number of patients reported to respond well to oral prednisone, rituximab, and daclizumab

DIF, Direct immunofluorescence; *EM,* erythrema mulitforme; *H&E,* hematoxylin-eosin staining; *IIF,* indirect immunofluorescence.
[a] Off-label.

autoimmune diseases; one well described is neonatal lupus. PV[82] (termed neonatal pemphigus or pemphigus neonatorum), EBA,[83] BP,[84,85] pemphigus vegetans,[86] and PF[87–90] have been reported to be transmitted in this fashion. Vertically transmitted autoimmune conditions are caused by passive transfer of IgG antibodies, which are able to cross the placenta beginning at week 13 and are present at highest levels in the third trimester.[86,91,92]

What are the clinical differences between the newborn with neonatal pemphigus and the affected mother?

Neonatal pemphigus presents at birth, or at up to 2 weeks of age,[93] with vesicles and erosions on the trunk and extremities. Mucous membrane involvement is less common than in adults,[94] which is a notable distinction. The more diffuse distribution of lesions in neonatal pemphigus compared with the adult form, which has primarily mucosal involvement, is thought to be due to the differing distribution of desmogleins in the neonate versus the adult. Neonates have more diffusely distributed desmoglein-3, which is the primary target in PV.[95–97] In adults, desmoglein-3 is localized to the mucous membranes and the deep epidermis, whereas desmoglein-1 is localized to the more superficial epidermis, specifically the granular layer; hence, adults with antibodies only against desmoglein-3 will have disease localized to the mucosa because the unaffected desmoglein-1 can maintain the integrity of the skin.[98,99]

The majority of newborns with neonatal pemphigus are born to mothers with clinical symptoms; however, it has been reported in mothers in clinical remission.[100,101] Antibody titers in the mother have ranged from 1:20 to 1:640, and several authors suggest that neither antibody titers nor the clinical severity of the mother's findings predict the severity of disease in the child.[99,102,103] All the cases of intrauterine fetal death and growth retardation have been described in mothers with severe clinical disease.[96] This finding suggests that pathogenesis is multifactorial and that too few cases have been described to predict fetal outcome. Affected infants' skin disease resolves within weeks and may require treatment with topical antibiotics, topical corticosteroids, or supportive care only with bland emollients.[95,102]

Ruach et al[96] suggest that conception be timed during a period of clinical remission with low immunofluorescence titers. The authors also recommend fetal screening with surveillance sonography, fetal movement counting, and repeat nonstress tests during the latter period of pregnancy.[96] Caesarian section is not of benefit given increased infection risks, so vaginal delivery is recommended unless labor complications occur.[96,104]

Pemphigus foliaceus has also rarely presented in newborns of mothers with clinical disease.[87] It is caused by transmission of IgG antibodies primarily against

desmoglein-1.[88] Mothers in clinical remission have delivered unaffected infants in reported cases.[89] It has been suggested that a higher maternal antibody titer may need to be surpassed before neonatal involvement occurs,[90] but too few cases have been reported for conclusions to be drawn.

What is a major difference in treating an immunobullous disease in neonates versus their affected mothers?

Because neonates with an immunobullous disorder are affected due to transplacental passage of maternal IgG autoantibodies, care is generally supportive with bland emollients such as petrolatum and topical corticosteroids if needed. Disease activity will likely wane as maternal autoantibodies are cleared from the affected neonate. New blisters rarely develop past the newborn period.[95,102]

What are the clinical features of pemphigoid gestationis in the pregnant woman and her newborn?

Pemphigoid gestationis (PG), previously known as herpes gestationis, is a very rare autoimmune dermatosis specific to pregnancy. It presents during pregnancy as periumbilical annular urticarial plaques that can spread to flexural areas and can vesiculate.[105] Affected women are usually in their second or third trimester; however, it can present in the postpartum period as well. PG is unique in that it presents during pregnancy in clinically unaffected women and remits either immediately postpartum or within weeks to months of delivery. It can recur with subsequent pregnancies. Babies are affected due to transfer of pathogenic antibodies to a subunit of bullous pemphigoid antigen. It is associated with adverse birth outcomes, including miscarriage, low birth weight, prematurity, and transient redness or blistering.[105–107] Clinically, the presence of blisters in the mother has been associated with decreased gestational age; the earlier the onset of disease, the higher the risk of prematurity and low birth weight in the infant.[108] These patients should be followed closely with high-risk obstetric care. PG is treated symptomatically, most commonly with topical corticosteroids and systemic prednisone. The risks of prednisone to the fetus and the risks of disease sequelae must be carefully weighed.

Which autoimmune bullous diseases have been reported to present as mimickers of child abuse?

Clinicians should be aware that certain immunobullous disorders (LABD, bullous pemphigoid, EBA, pemphigus) may present in the genital region.[109,110] Linear IgA disease, for example, has a predilection for the anogenital region in children. The genital area may be the only site of involvement, making the diagnosis challenging, especially for nondermatologists. Localized genital BP is one very rare subtype of childhood BP that can be mistaken for child abuse. This variant is much more common in girls and has a favorable prognosis with good response to high-potency topical corticosteroids.[111] Vulvar-only cicatricial pemphigoid has also been reported in an 11-year-old girl after undergoing evaluation to rule out child sexual abuse.[112]

What are the differences in antibiotic choices for adults versus children when treating autoimmune bullous diseases?

Systemic antibiotics may aid in the treatment of autoimmune bullous diseases, which is thought to be due to their antiinflammatory properties. One benefit of a trial of antibiotics in treatment of children with bullous disorders is that there is often not a need for bloodwork or ongoing laboratory monitoring. Although there are risks of antibiotic resistance, allergic reactions, and gastrointestinal side effects, the lack of systemic immunosuppression can also prove beneficial for both children and adults.

Antibiotics that have been reported to be helpful in the management of bullous disorders include the tetracyclines[21,22]; however, they are contraindicated in children younger than age 8 years because they cause permanent dental staining of secondary teeth. Erythromycin has been reported to be helpful in LABD, BP, and bullous systemic lupus erythematosis[18,19,113,114] and is often tried in pediatric patients with bullous disorders. In addition to antiinflammatory properties, it may increase serum levels of corticosteroids and have a steroid sparing effect when used in combination. Successful treatment with dicloxacillin and oxacillin has also been described.[59] Although trimethoprim-sulfamethoxazole has also been reported to be used successfully in CBDC/linear IgA disease,[115] the potential for severe allergic reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis, must be weighed against the potential benefits. Also, bloodwork is recommended for this antibiotic choice; complete blood cell count with differential should be checked at baseline and is recommended to be monitored monthly in patients receiving long-term therapy.[116] Hemolytic anemia is a side effect in patients with G6PD deficiency. In women of child-bearing age a baseline pregnancy test is also indicated because trimethoprim-sulfamethoxazole is a pregnancy category C drug.

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