Linear IgA Bullous Dermatosis in Adults and Children: A Narrative Review of Literature on Disease Distribution and Evaluation of Existing Scoring Tools

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SUMMARY Linear IgA Bullous Dermatosis (LABD) is a rare autoimmune blistering disease (AIBD) characterized by linear depositions of IGA antibodies at the dermo-epidermal junction, resulting in subepithelial vesiculobullous lesions that affect the skin and mucous membranes. Despite advancements in the study of AIBDs, significant gaps persist in LABD's clinical presentation, treatment, and outcome measures due to the absence of validated, disease-specific scoring systems. The purpose of this paper is to identify any differences in disease distribution between adults and children, and to review and evaluate existing scoring tool for AIBDs. A literature search was performed using Embase and PubMed to identify relevant studies and case reports. According to the literature, adults and children had different cutaneous distributions of disease, with lesions on the perineum, hands and feet, and face more frequently reported in children. However, there was inconsistent data on whether mucous membrane lesions were more frequent in adults or children. Current scoring systems for AIBDs were also identified, with several systemic scoring systems existing in the literature that are validated in scoring AIBD severity. There is currently no literature on scoring systems specific to LABD, underscoring the need to develop and validate LABD specific tools to facilitate the development of standardized treatment guidelines and advance the understanding and management of LABD.

KEY WORDS: Linear IgA bullous dermatoses, chronic bullous disease of childhood, treatment and outcomes, disease severity, scoring system

INTRODUCTION

Linear IgA bullous dermatosis (LABD) is a rare autoimmune blistering disease (AIBD) affecting the skin and mucous membranes (Table 1). Clinical presentation is dependent on the age of the patient, with adults and children presenting with different disease distributions (1). Whilst prognosis is generally good, disease duration can last anywhere between 1-15 years, with spontaneous relapses posing considerable morbidity rates and negative impacts on the patients' quality of life (2). Currently, validated scoring systems for AIBDs are used to perform multi-centered controlled trials for new therapeutic advancements (3). However, there is a lack of standardized and validated outcome measures specific to LABD, resulting in a shortage of new treatments and the absence of formal management guidelines (4). This review aims to identify the clinical difference between LABD in adults and children and evaluate the existing scoring systems available for AIBDs to assess disease severity.

METHODS

A literature review was performed in February 2025 across Embase and PubMed. The following search terms "linear IGA bullous dermatoses" or "chronic bullous disease of childhood" or autoimmune bullous disease" were used with "clinical feature", "disease severity", "scoring system", "outcome assessment" and "patient acuity". There were no restrictions on the date published and language, provided an English translation could be obtained. Animal studies were excluded, and duplicates were removed. The citation list of these articles was also reviewed for further relevant studies. An abstract screen was then performed, and articles were removed if LABD or scoring systems were not mentioned. Full versions of the articles were then retrieved and reviewed as seen in Figure 1.

DISEASE OVERVIEW

LABD is a subepithelial vesiculobullous disease characterized by linear depositions of IgA antibodies at the dermo-epidermal junction, resulting in blisters and erosions on the skin and mucous membranes. It can occur in both adults and children, with its childhood manifestation known as "chronic bullous disease of childhood" (5). LABD was first described in 1901 but was not recognized as a separate entity from dermatitis herpetiformis until 1979 when direct immunofluorescent (DIF) allowed for the visualization of basement membrane zone (BMZ) specific IgA deposited in a linear pattern (6, 7). This is thought to be caused by the production of IgA autoantibodies against 97kDa and LAD-1 fragments of bullous pemphigoid antigen 2 (BPAG2), thus triggering both humoral and cellular responses. This process leads to

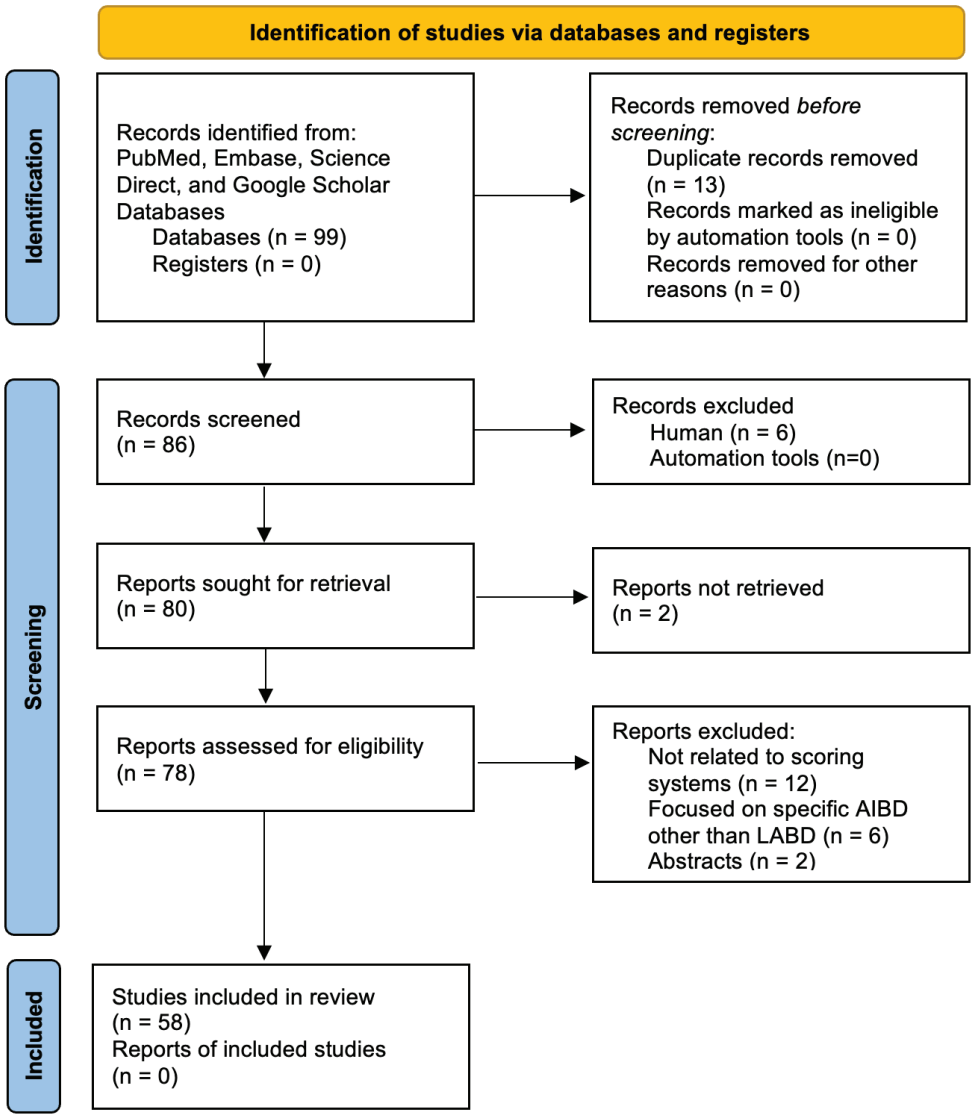

Figure 1. Diagram of a literature search for AIBD/LABD outcome measure publications. Created using Prisma Flowchart(56)

the degradation of BMZ components, and the subsequent blister formation (4, 8).

Epidemiology

LABD is a rare disease varying from 0.2 to 2.3 cases per million individuals per year based on geographical location(8). In Western Europe, the incidence rate is 0.5 per million, though it is more commonly observed in Chinese, Southeast Asian, and African populations (4). It demonstrates a bimodal age distribution, occurring during childhood between 6 months to the age of 10 and in late adulthood after the age of 60 (9). There is no established gender or ethnicity predominance for LABD with epidemiological studies of both adult and child variants showing significant variability (8-10).

Etiology

The primary underlying etiology of LABD is the development of circulating IgA autoantibodies against proteins in the BMZ, which can arise idiopathically or from a range of environmental influences (11). Drug-induced LABD is a frequent trigger in adults with vancomycin being responsible for 56% of cases reported in literature (12). Other implicated drugs include antibiotics, phenytoin, non-steroidal anti-inflammatory agents, and antihypertensives. More recently, case reports have also linked the onset of LABD to COVID-19 vaccinations (13, 14). Genetic predispositions of human leukocyte antigen types, such as HLA-B8, HLA-DR3, HLA-DQ2, and HLA-cw7, and various autoimmune diseases such as ulcerative colitis, can also be associated with the disease (12, 15-17).

Clinical Features

Clinical manifestations of LABD can occur on both mucosal and cutaneous surfaces and often mimic bullous pemphigoid (BP) (8). Patients present with tense, clear or hemorrhagic bullae or vesicles of various sizes, sometimes on a background of erythema or urticaria, as shown in Figure 2. The lesions also frequently coalesce into annular plaques with a ring of blisters and vesicles, creating the characteristic "string of pearls" pattern (9, 18, 19).

The patient has provided informed consent for the publication of his photographs in Figure 2.

The distribution of these lesions differs between the adult variant and the child variant (9). Whilst cutaneous lesions primarily affected the trunk and limbs in both variants, existing literature supports that the childhood variant had more frequent involvement of the perineum, hands and feet, and face, especially in the perioral area (9, 19-21). In addition, the "string of pearls" pattern was more commonly observed in children (10, 22).

Mucosal lesions, particularly affecting the oral and conjunctival surfaces, have also been noted in LABD patients. However, data on the prevalence of mucosal involvement are inconsistent between the childhood and adult variants, with studies reporting from 40% of cases up to 80% of cases (21, 23). Several large-scale case studies have documented more frequent mucosal involvement in adults compared to children, with Horiguchi *et al.* reporting that 3.8% of LABD cases with mucosal involvement were associated with the childhood variant (9, 19, 21, 24, 25). This was contradicted by Genovese *et al.* who found that mucosal involvement was more frequently involved in children

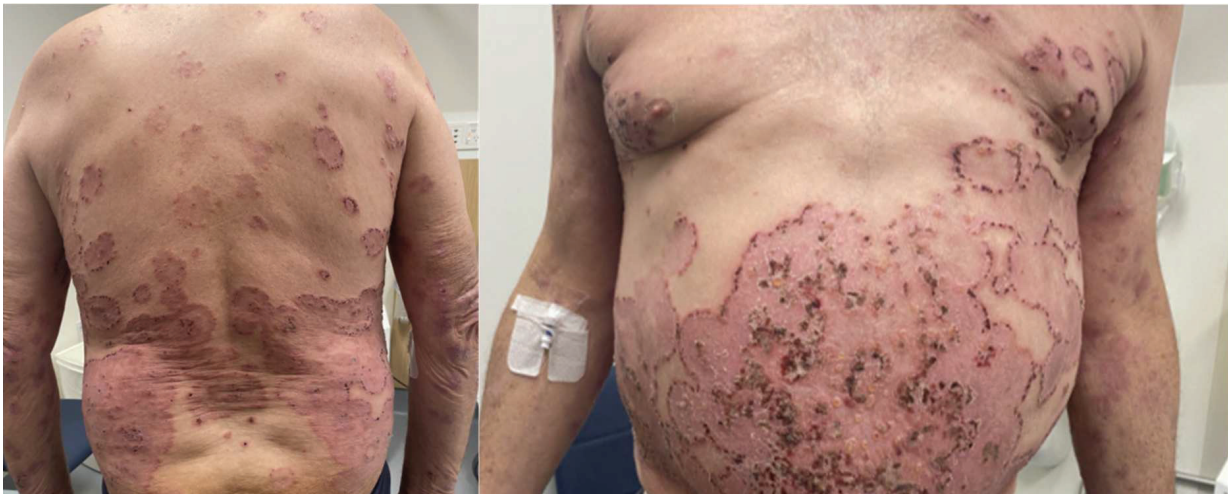

Figure 2. Clinical manifestations of LABD on adults. Erythematous, crusting bullae and plaques on the trunk

(45.5%) than adults (14.8%) (10, 22). However, these discrepancies can be attributed to the retrospective case study method that resulted in different adult and children sample sizes, introducing recall and selection bias (26). Thus, a more systematic analysis is required to provide a more accurate understanding of the disease's mucosal manifestations.

Diagnosis

Diagnosis for LABD is based on three different parameters: clinical, histopathological, and immunological(8). Following the confirmation that clinical manifestations are concurrent for those with LABD, a biopsy for DIF is the current gold standard for diagnoses. A positive diagnosis can be made if solely linear deposits of IgA are found along the BMZ. In the case that both IgA and IgG deposits are found, the fluorescent intensity of IgA must be stronger than that of IgG to differentiate LABD from other subepidermal AIBDs (27). In the case of a negative DIF, an indirect immunofluorescence microscopy on salt split-skin or a western blot can be performed for confirmation (8, 27).

Treatment

Despite a lack of large, randomized controlled trials (RCT) on the treatment of LABD, systemic treatments have shown to be effective in both adults and children (8, 27). As many cases of LABD are drug-induced, identification and cessation of the drug should be considered as the first step in management. Dapsone, an antibiotic and anti-inflammatory agent, is considered as the first-line therapy(28). However, before the initiation of dapsone, patients must be tested for glucose-6-phosphate dehydrogenase deficiency as it can result in life-threatening hemolysis (4). Other adverse effects include methemoglobinemia, jaundice, bone marrow suppression, hypersensitivity reactions, and motor peripheral neuropathy. In the case of dapsone intolerance or allergy, corticosteroids such as clobetasol propionate and prednisolone can be used, although efficacy remains variable as reported by Machado *et al.* (29). Adverse effects associated with long-term steroid use including Cushing's syndrome, infections, osteoporosis, cataracts, hyperlipidemia, and hyperglycemia have also been noted and must be monitored during the treatment period (2, 4, 29). Rituximab, an anti-CD20 monoclonal antibody, is an off-label treatment for LABD that has been increasingly used in recent years {Shin, 2021 #1} (2). 3 case studies reported the successful use of rituximab in severe LABD (30-32). Other treatments include, intravenous immunoglobulin, colchicine, erythromycin, mycophenolate mofetil, methotrexate, and cyclosporine. However, the usage of these treatments is mostly anecdotal case reports and further research with large-scale RCTs still needs to be conducted in this area (4).

Table 1. Abbreviations

Abbreviation	Description
ABSIS	Autoimmune bullous skin disorder intensity score
AIBD	Autoimmune blistering disease
BMZ	Basement membrane zone
BP	Bullous pemphigoid
BPDAI	Bullous pemphigoid disease area index
BPAG2	Bullous pemphigoid antigen 2
BSA	Body Surface Area
DIF	Direct immunofluorescent
HLA	Human leukocyte antigens
IGA	Investigator global assessment
LABD	Linear IgA bullous dermatosis
PDAI	Pemphigus disease area index
RCT	Randomized control trials

Scoring Systems

Validated scoring systems in dermatology provide standardized measures on disease severity and therapeutic outcomes which is crucial in reliable clinical trials (33-35). Currently, generic assessments such as the IGA are a preferred method to evaluate primary endpoints, however, disease-specific scoring systems have been proven to provide better accuracy and sensitivity (35, 36). A systematic review in 2006 highlighted the shortage of high-quality clinical trials for pemphigus treatment, attributing it to a lack of universally accepted outcome measures (37). This resulted in the development and validation of the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and the Bullous Pemphigus Disease Area Index (BPDAI) (3, 38, 39). To date, no validated scoring system exists for LABD, and non-specific assessment tools such as ABSIS and BPDAI are currently utilized in its evaluation. This highlights the need for disease-specific, validated scoring systems that account for its diverse clinical presentations to facilitate more robust clinical trials and outcome assessments.

Autoimmune Bullous Skin Disorder Intensity Score

The ABSIS is a generic scoring system developed in 2007 by the German Blistering Group to quantify small changes in disease severity for AIBDs. The scores can range from 0 to 206 relating to cutaneous lesions, oral involvement, and subjective discomfort (39). The skin score used the rule of 9s to assess the percentage

of body surface area (BSA) affected by blisters and erosions and the oral mucosal involvement scoring assessed the extent (presence of lesions) and severity of symptoms (discomfort during eating/drinking different liquids and solid foods) (39-41). A study of 15 pemphigus patients by Rosenbach *et al.* found a high overall inter-rater reliability, however, it was mainly attributed to the subjective component, thus suggesting the ABSIS was less effective in capturing the severity and extent of cutaneous lesions (42). This could be due to the small patient pool mainly including patients with mild to moderate pemphigus who had undergone treatment, indicating the need for large, well-defined population studies for further validation (43). As a result, in 2018, a large international multi-center study involving 116 pemphigus patients over 24 months was performed and showed that the ABSIS had a high inter-rater reliability at baseline and follow up, and performed better in intermediate and extensive cases, with the skin activity sub scores correlating with the decrease of disease-specific antibodies(38, 44). Both studies noted the limitations of the ABSIS including "the rule of 9" to calculate BSA which can be inaccurate, and its lack of inclusion for mucous membranes other than oral (38, 42, 45). Overall, these findings underscore that the ABSIS is an accurate tool in assessing pemphigus. However, further research is needed to assess its validity in other AIBDs including LABD.

Bullous Pemphigoid Disease Area Index

The BPDAI is a scoring system developed in 2007 by the International Bullous Diseases Group to assess disease activity in patients with BP. It has a range of score between 0-360 for disease activity (number of blisters/erosions, active urticaria/erythema patches, and hyperpigmentation) in each of the top 12 areas of mucosal involvement (3, 44). Pruritus is measured separately as a subjective component(3). The BPDAI has been validated as a robust assessment tool for scoring the severity of BP with a single center study in 2012 showing a correlation of the BPDAI score with the serum anti-BP180 autoantibody titers, which was in accordance with previous literature (46, 47). Furthermore, in 2021, a multi-center study involving 285 BP patients demonstrated a high inter-rater reliability (ICC>0.9) for all severity subgroups up until the 6 months follow-up mark, suggesting that the BPDAI can accurately assess BP activity both at baseline and during the disease course (44, 48).

In a comparison between the ABSIS and BPDAI score, BPDAI was found to have a higher inter-rater reliability and precision score, which could be attributed to the limitations of the ABSIS score as mentioned above (49, 50). Nevertheless, both scoring systems had high intra-rater reliabilities (ICC>0.99) and were superior to the Physician Global Assessment (PGA) score (49).

BP and LABD are both subepidermal blistering skin diseases and present with tense bullae on cutaneous and mucosal surfaces. Due to their clinical similarities, the BPDAI has been proposed as a potential scoring system for LABD with slight modifications made to better reflect the lesion distribution specific for LABD (including axillae and groin)(50). However, it is important to note that no studies to date have validated its application in LABD, underscoring the need for further research in this area.

Pemphigus Area and Activity Score (PDAI)

The PDAI is a scoring system published in 2008 to assess the extent of pemphigus disease. It has a potential score ranging from 0-263, evaluating activity and damage associated with the skin, scalp, and mucous membranes (34, 41, 44). The initial study by Rosenbach *et al.*, showed that the PDAI was a better representation of true clinical severity and had greater reproducibility rates compared to ABSIS as it was sensitive to small changes in disease severity (42). Due to the limitations of the methodology – the two-hour time gap between subsequent assessments was not enough to prevent recall bias and the cohort mainly consisted of mild-moderate pemphigus patients – an international multi-center study was later conducted which underscored that both PDAI and ABSIS were reliable and valid in assessing pemphigus severity (38, 42, 51). The PDAI was also later modified into the BPDAI which was more specific for BP(3). However, as clinical presentations of LABD mirror those of BP, the BPDAI scoring system is potentially more suitable as an assessment tool compared to PDAI.

Global Assessments

Global assessments are simple outcome measures that score the overall severity of a disease on an ordinal scale (3). The IGA is the most well-known global assessment and is a 5-point scale ranging from 0 to 4 (0=clear to 4=severe) and scores cutaneous and mucosal lesions separately, which provides a simplistic and clinically meaningful measure for both patients and clinicians (44, 51). However, compared to other assessment tools such as ABSIS and BPDAI, IGAs are more subjective with high inter-rater variabilities, indicating the possibility of inconsistencies between scorers (52). Despite this, the US Food and Drug Administration (FDA) prefers the use of global assessments such as the IGA as primary endpoints of

clinical drug trials, with IGAs having been developed and validated for more common dermatological conditions such as atopic dermatitis, psoriasis, and acne vulgaris (3, 53-55). Developing and validating an IGA for LABD will thus aid in the approval of clinical drug trials to further advanced treatment options.

CONCLUSION

Despite advancements in the study of AIBDs, significant gaps and inconsistencies persist in its clinical presentation, treatment, and outcome measures due to a lack of robust evidence from large-scale RCTs. Validation of scoring systems on disease severity allows for accurate comparison between patients and their responsiveness to treatment and thus are essential clinical trials. Currently, the absence of disease-specific, validated scoring systems for LABD hinders the ability to conduct high-quality clinical trials and develop standardized treatment guidelines. Thus, further research into developing and validating such scoring systems, including evaluating the validity and reliability of LABD-specific IGAs, is required to address these gaps.

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