



An In-Depth Understanding of The Pathophysiology and Therapeutic Approaches to Chronic Bullous Disease of Childhood (CBDC)

Tassa Nasirah*, Cut Putri Hazlianda

Universitas Sumatera Utara, Indonesia

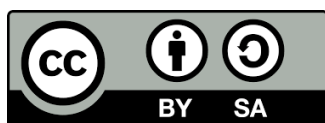
Email: tassanasirahh@gmail.com*

Keywords:

Chronic Bullous Disease of Childhood; Linear IgA Bullous Dermatitis; Autoimmune Disease; Immunoglobulin A; Therapeutic Management

Abstract

Chronic bullous disease of childhood (CBDC), also known as childhood linear IgA bullous dermatosis, is a rare autoimmune blistering disorder characterized by subepidermal blister formation and linear immunoglobulin A (IgA) deposition along the basement membrane zone. Its heterogeneous clinical presentation and similarities to other autoimmune blistering disorders pose diagnostic and therapeutic challenges. This study aimed to synthesize current evidence regarding the pathophysiology, clinical manifestations, diagnostic approaches, and therapeutic management of CBDC. A descriptive literature review was conducted using relevant original research articles, case reports, review articles, and clinical guidelines. The literature was organized thematically and comparatively evaluated to identify consistent findings, variations in clinical presentation, and limitations in the available evidence. The reviewed studies identified IgA autoantibodies targeting components of the dermal–epidermal junction, particularly BP180 (type XVII collagen), as important contributors to inflammatory responses and subepidermal blister formation. Clinical manifestations included tense vesicles and bullae, frequently exhibiting a characteristic "string of pearls" arrangement, with variable mucosal involvement. Direct immunofluorescence (DIF) examination of perilesional skin remained essential for diagnostic confirmation because clinical and histopathological features could overlap with those of other blistering disorders. Dapsone was identified as a first-line treatment, while systemic corticosteroids and alternative therapeutic agents were considered according to disease severity, treatment response, and tolerability. However, the predominance of observational evidence limited definitive comparisons of treatment effectiveness and safety. In conclusion, CBDC requires a comprehensive diagnostic approach and individualized therapeutic management. Further prospective pediatric studies are needed to strengthen the evidence regarding treatment efficacy, safety, recurrence, and long-term clinical outcomes in affected children.



This is an open access article under the [CC BY-SA](https://creativecommons.org/licenses/by-sa/4.0/) license.

Copyright © 2026 by Author. Published by Publikasi Indonesia

INTRODUCTION

Chronic bullous disease of childhood (CBDC), also known as childhood linear IgA bullous dermatosis (LABD), is a rare autoimmune blistering disorder characterized by subepidermal blister formation and linear deposition of immunoglobulin A (IgA) along the dermal–epidermal junction. Although uncommon, CBDC is considered one of the most frequently occurring autoimmune blistering disorders in children. Clinically, it primarily affects infants and young children, presenting with tense vesicles and bullae on an erythematous base.

The lesions often develop a characteristic annular arrangement, commonly described as a "string of pearls" or "cluster of jewels" pattern (Damayanti et al., 2020; Mellyanawati, 2021; Yadav et al., 2026).

CBDC typically develops in children between 6 months and 10 years of age, with a reported mean age of onset of approximately 4.5 years. The annual incidence of linear IgA bullous dermatosis has been estimated at approximately 0.5 cases per million population in parts of Western Europe. Higher frequencies have been reported in certain regions, including China, Southeast Asia, and Africa, although geographical differences in epidemiological data remain incompletely understood. Linear IgA bullous dermatosis exhibits a bimodal age distribution, with peaks during early childhood and in adults older than 60 years. Some studies have reported a slight female predominance in childhood cases, although the overall sex distribution appears relatively balanced (Khan et al., 2023; Pradhan et al., 2022).

The pathogenesis of CBDC involves the production of IgA autoantibodies directed against structural proteins at the dermal–epidermal junction, particularly BP180, also known as type XVII collagen. These autoantibodies promote inflammatory responses characterized by neutrophil recruitment and subsequent subepidermal blister formation (Bernett et al., 2023; do Vale et al., 2019; Kowalewski & Wozniak, 2025; Onalaja-underwood et al., 2024). Other antigenic targets, including BP230, LAD285, type VII collagen, and additional dermal proteins, have also been reported, reflecting the immunological heterogeneity of the disease. The pathogenesis of drug-induced linear IgA bullous dermatosis remains incompletely understood. One proposed mechanism involves drug-related alterations in antigen recognition that trigger an autoimmune response against cutaneous proteins. In vancomycin-associated cases, IgA autoreactivity against the noncollagenous 1 (NC1) domain of type VII collagen has been reported, although this finding does not establish a universal mechanism for drug-induced disease (Pradhan et al., 2022).

The clinical manifestations of linear IgA bullous dermatosis vary between pediatric and adult populations. In children, the mean age of onset is generally reported to be approximately four to five years. The disease commonly presents as an acute eruption of tense vesicles and bullae, accompanied by pruritus or a burning sensation of variable intensity. Frequently affected areas include the face, perineum, lower abdomen, genital region, thighs, and buttocks, with possible extension to the extremities. Morphologically, lesions may develop on erythematous or urticarial plaques in annular or polycyclic arrangements, with peripheral vesicles and bullae producing the characteristic "string of pearls" appearance. Some lesions may enlarge or become hemorrhagic. Mucosal involvement may manifest as oral erosions or ulcerations, ocular inflammation, and symptoms affecting the nasal or upper respiratory mucosa. Reported frequencies of mucosal involvement vary across studies and patient populations, with some estimates ranging from approximately 60% to 80%. In adults, the characteristic annular arrangement may be less prominent, while ocular involvement, nasal symptoms, and hoarseness associated with possible laryngeal involvement may occur (Wilson & Murrell, 2022).

The diagnosis of CBDC requires correlation between clinical presentation, histopathological findings, and immunopathological examination because routine histological features are not disease-specific. Histopathological examination typically reveals subepidermal blister formation accompanied by inflammatory cell infiltration, frequently with a predominance of neutrophils. Eosinophil-rich infiltrates may resemble those observed in

bullous pemphigoid, whereas neutrophilic microabscesses within the dermal papillae may resemble dermatitis herpetiformis. Therefore, direct immunofluorescence (DIF) examination is essential for diagnostic confirmation. Skin biopsy specimens for DIF should preferably be obtained from clinically unaffected perilesional skin adjacent to an active lesion. The characteristic finding is a continuous linear deposition of IgA along the basement membrane zone, although additional immunoreactants may occasionally be detected (Caux et al., 2024; Feng et al., 2025; Nasri et al., 2022; L. Shin et al., 2021; Stoj & Lu, 2022) .

The diagnostic complexity of CBDC is closely associated with its immunopathogenesis. IgA autoantibodies recognize structural proteins involved in maintaining adhesion at the dermal–epidermal junction, particularly antigens associated with BP180 (type XVII collagen). Antibody-mediated inflammatory responses contribute to dermal–epidermal separation and subsequent blister formation. However, variations in antigen recognition indicate that linear IgA bullous dermatosis is immunologically heterogeneous rather than a uniform autoimmune disorder. European guidelines on linear IgA bullous dermatosis emphasize the importance of immunopathological findings in establishing the diagnosis and guiding clinical assessment (Caux et al., 2024). Integrating these immunological mechanisms with clinical manifestations and laboratory findings provides a foundation for understanding the relationship between disease pathophysiology and therapeutic management.

Research on therapeutic approaches has improved understanding of available management strategies, although the quality and consistency of supporting evidence remain limited. (S. Shin et al., 2021), in a systematic review, examined developments in the diagnosis and treatment of linear IgA bullous dermatosis and highlighted the importance of considering patient age, comorbidities, and disease severity when selecting treatment. Their findings supported the consideration of alternative therapies when conventional treatment was contraindicated, poorly tolerated, or ineffective, while acknowledging limitations in the available literature. More recently, (Caux et al., 2024) published European guidelines addressing the diagnosis and management of linear IgA bullous dermatosis. Therefore, the principal research challenge is not the complete absence of clinical recommendations but the need to interpret existing guidance in the context of limited pediatric-specific evidence and individual patient characteristics.

Despite these developments, substantial evidence gaps remain regarding the management of CBDC. Available pediatric studies consist predominantly of case reports and small case series, limiting reliable comparisons between therapeutic interventions and reducing certainty regarding long-term clinical outcomes (Mori et al., 2022). Furthermore, studies combining pediatric and adult populations may obscure age-related differences in disease presentation, treatment response, and medication safety. These limitations highlight the need for a focused synthesis that distinguishes evidence derived directly from children from findings obtained in adult or mixed-age populations. Accordingly, the research gap addressed in this review concerns the fragmented integration of immunopathological mechanisms, clinical manifestations, diagnostic confirmation, and therapeutic decision-making rather than the absence of previous research or published clinical recommendations.

Addressing these limitations is clinically important because diagnostic uncertainty and therapeutic complexity affect a pediatric population requiring careful consideration of medication safety and tolerability. Dapsone remains a principal treatment option for linear IgA

bullous dermatosis; however, its administration requires appropriate pretreatment assessment and monitoring for adverse effects, particularly hemolysis and methemoglobinemia, as emphasized in current clinical guidance (Caux et al., 2024). These considerations underscore the importance of balancing disease control against treatment-related risks, especially when prolonged therapy or additional immunomodulatory agents are required. A critical review may help distinguish management recommendations supported by clinical consensus from those based primarily on limited observational evidence. Such distinctions are essential for interpreting therapeutic outcomes without overstating their generalizability to pediatric patients.

In response to these challenges, this study aimed to provide a comprehensive descriptive literature review of CBDC by integrating evidence on epidemiology, immunopathogenesis, clinical manifestations, diagnostic approaches, and therapeutic management. Its primary contribution was to organize these domains according to their clinical relevance, particularly how autoimmune mechanisms contribute to blister formation, how characteristic manifestations guide diagnostic suspicion, and how diagnostic confirmation and disease severity inform treatment selection. Rather than proposing a new pathogenic mechanism or therapeutic intervention, the review sought to synthesize established knowledge and identify unresolved clinical questions. Its distinctive contribution was a pediatric-focused interpretation of the available literature, with particular attention to differences between evidence obtained from children and findings derived from adult or mixed-age populations.

Accordingly, the objectives of this review were to describe the principal immunopathological mechanisms underlying CBDC, summarize its clinical manifestations, explain the diagnostic importance of direct immunofluorescence, and critically examine available therapeutic options and their limitations. The review also aimed to identify priorities for future research, including standardized outcome reporting and stronger evidence regarding treatment efficacy, safety, recurrence, and long-term outcomes in pediatric populations. Its anticipated benefit was to provide an accessible scientific foundation for clinicians, researchers, and healthcare trainees seeking to understand this rare autoimmune blistering disorder. By integrating biological mechanisms, diagnostic considerations, and therapeutic evidence, the review sought to support evidence-informed clinical decision-making and encourage further research addressing the specific needs of children with CBDC.

METHOD

This study employed a descriptive literature review approach to examine the pathophysiology, clinical manifestations, diagnostic methods, and therapeutic management of chronic bullous disease of childhood (CBDC).

The literature was obtained from relevant scientific publications, including original research articles, case reports, narrative and systematic reviews, and clinical guidelines addressing CBDC, also known as childhood linear IgA bullous dermatosis (LABD). The sources analyzed were those included in the manuscript's reference list.

Relevant publications were identified and selected based on their relevance to the research objectives. Information extracted from the selected literature was organized into five main categories: disease characteristics and epidemiology, pathophysiology, clinical manifestations, diagnostic approaches, and therapeutic options.

The collected information was analyzed descriptively through comparative and thematic synthesis of findings from previous studies. The analysis focused on identifying similarities, differences, and developments in the understanding of CBDC, particularly its underlying mechanisms, diagnostic considerations, and therapeutic management. The findings were systematically synthesized to provide an integrated overview of the disease and inform conclusions regarding appropriate diagnostic and treatment approaches for pediatric patients with CBDC.

RESULTS AND DISCUSSION

Pathophysiology of Chronic Bullous Disease of Childhood

Based on the results of a literature review, Chronic Bullous Disease of Childhood (CBDC) is an autoimmune bull disease characterized by the formation of subepidermal bulls due to an autoimmune response to the structural components of the skin. The main mechanism of this disease is related to the formation of immunoglobulin A (IgA) autoantibodies that attack the basal membrane zone components, especially BP180 or collagen XVII.

The interaction between IgA autoantibodies and target antigens triggers an inflammatory response in the dermo-epidermal area. The process involves the infiltration of inflammatory cells, especially neutrophils, which cause damage to the basal membrane structure. This damage then results in the separation of the epidermal layer from the dermis and the formation of subepidermal vesicles or bules.

In addition to BP180, several other antigens such as BP230, LAD285, and collagen VII are also reported to play a role in the process of CBDC pathogenesis. However, the mechanism of involvement of these various antigens is still not fully understood. In some cases triggered by drug use, the mechanism of disease occurrence is also thought to involve the formation of an autoimmune response to skin proteins.

Clinical Manifestations

The results of the study showed that CBDC generally occurs in infants and children with an initial age range of about six months to ten years. The main clinical manifestations are strained vesicles and bules above the base of the skin with erythema. One of the most distinctive clinical characteristics is the pattern of string of pearls, cluster of jewels, or rings of pearls.

Skin lesions can be found on various parts of the body, especially the face, lower abdomen, perineal area, thighs, buttocks, hands, and feet. In addition to manifestations on the skin, some patients can also experience mucosal involvement. These involvements can be in the form of ulceration or erosion of the mucosa, disorders in the nasal area, and manifestations in the eyes.

The presence of a distinctive pattern of lesions can help direct the diagnosis of CBDC. Nevertheless, the clinical picture of the disease can resemble that of some other bully diseases. Therefore, the diagnosis cannot be established based solely on clinical examination, but requires appropriate supporting examinations.

Diagnosis CBDC

Enforcement of the diagnosis of CBDC requires the integration of anamnesis, clinical examination, histopathological examination, and immunopathological examination. Histopathological examination generally shows the presence of subepidermal bulbules

accompanied by the infiltration of inflammatory cells. However, these findings are not specific because they can resemble other autoimmune bullous diseases.

Direct immunofluorescence (DIF) examination is one of the most important examinations in establishing the diagnosis. This examination is carried out using perilesional skin samples that are relatively not severely damaged. A typical result of CBDC is the discovery of IgA deposition with a linear pattern in the basal membrane zone.

These findings have an important role in differentiating CBDCs from other diseases, such as pemphigoid bullosa and dermatitis herpetiformis. Therefore, the use of DIF is urgently needed to improve the accuracy of diagnosis and determine appropriate management approaches.

Therapeutic Approach

Based on the results of the study, the management of CBDCs still has challenges because the available therapy options need to be tailored to the clinical conditions and patient responses. Various therapies have been reported in previous studies, mainly based on case reports and observational studies.

The therapy used aims to control the formation of new lesions, reduce inflammatory processes, overcome the symptoms experienced by the patient, and prevent complications. Dapsone is known as one of the main therapeutic options in the management of this disease. In addition, corticosteroids and some additional therapies can be used in certain conditions, especially if the patient does not respond optimally to the initial therapy.

The selection of therapy should take into account the severity of the disease, the extent of skin and mucosal involvement, the age of the patient, and the likelihood of side effects. These conditions indicate that the CBDC therapy approach needs to be carried out individually according to the characteristics of each patient.

Analysis and Clinical Implications

Overall, the results of the study show that CBDC is an autoimmune disease that has complex clinical characteristics and pathogenesis mechanisms. The formation of IgA autoantibodies against basal membrane components is an important factor in the occurrence of inflammatory processes and the formation of blisters.

Proper diagnosis is very important because this disease has similarities with various other bullous dermatoses. Direct immunofluorescence examination has a very important role in ensuring diagnosis through the identification of linear IgA deposition patterns in the basal membrane zone.

Although various treatment options are available, not all aspects of CBDC management have uniform standards. Therefore, a comprehensive understanding of clinical conditions and disease mechanisms is needed in order to make appropriate therapeutic selection. Further studies on the effectiveness and safety of various therapeutic approaches are also needed to support the development of more optimal CBDC management strategies.

CONCLUSION

This descriptive literature review highlighted chronic bullous disease of childhood (CBDC) as a rare autoimmune blistering disorder requiring an integrated understanding of its immunopathogenesis, clinical manifestations, diagnostic characteristics, and therapeutic management. Immunoglobulin A (IgA) autoantibodies targeting components of the basement

membrane zone, particularly BP180-associated antigens, contribute to inflammatory responses and subepidermal blister formation. Although annular lesions exhibiting the characteristic "string of pearls" pattern may support clinical suspicion, variations in clinical presentation and similarities to other autoimmune blistering disorders underscore the importance of direct immunofluorescence (DIF) for diagnostic confirmation. Dapsone remains a principal therapeutic option, while alternative or adjunctive treatments should be selected according to disease severity, mucosal involvement, therapeutic response, and patient safety. Although existing clinical guidelines provide a foundation for disease management, the predominance of case reports and small observational studies limits the strength of evidence regarding comparative treatment efficacy, long-term safety, and clinical outcomes in pediatric patients.

Future research should prioritize prospective multicenter studies and collaborative pediatric registries to improve understanding of the epidemiology, clinical progression, and therapeutic outcomes of CBDC. Standardized diagnostic criteria and clinical outcome measures are necessary to facilitate meaningful comparisons of disease control, recurrence, adverse drug reactions, and health-related quality of life across different treatment approaches. Further investigations should distinguish pediatric-specific findings from evidence derived from adult populations and examine the potential influence of age, autoantibody specificity, and mucosal involvement on disease prognosis and treatment response. Additional research into the immunopathological mechanisms underlying idiopathic and drug-induced CBDC may contribute to the identification of clinically relevant biomarkers and potential therapeutic targets. Collectively, these efforts could strengthen the evidence base for individualized treatment decisions and promote safer, more consistent, and evidence-informed care for children with CBDC.

REFERENCES

- Bernett, C. N., Fong, M., Yadlapati, S., & Rosario-Collazo, J. A. (2023). Linear IGA Dermatitis. In *StatPearls*.
- Caux, F., Patsatsi, A., Karakioulaki, M., Antiga, E., Baselga, E., & Borradori, L. (2024). S2k guidelines on diagnosis and treatment of linear IgA dermatosis initiated by the European Academy of Dermatology and Venereology. *Journal of the European Academy of Dermatology and Venereology*, 38, 1006–1023.
- Damayanti, N., Irmawati, Y. E., Radiono, S., Widodo, Y., & Dwianingsih, E. K. (2020). Chronic Bullous Disease of Childhood: Tinjauan Klinis, Histopatologi, dan Direct Immunofluorescence Pada Penegakan Diagnosis. *Media Dermato-Venereologica Indonesiana*, 49(3).
- do Vale, E. C. S., Dimatos, O. C., Porro, A. M., & Santi, C. G. (2019). Consensus on the treatment of autoimmune bullous dermatoses: dermatitis herpetiformis and linear IgA bullous dermatosis – Brazilian Society of Dermatology. *Anais Brasileiros de Dermatologia*, 94, 48–55.
- Feng, X., Zheng, H., Wang, M., Wang, Y., Zhou, X., & Zhang, X. (2025). Autoimmune bullous diseases: pathogenesis and clinical management. *Molecular Biomedicine*, 6. <https://doi.org/10.1186/s43556-025-00272-9>
- Khan, M., Park, L., & Skopit, S. (2023). Management Options for Linear Immunoglobulin A (IgA) Bullous Dermatitis: A Literature Review. *Cureus*, 15(3).

- Kowalewski, C., & Wozniak, K. (2025). Linear IgA bullous dermatosis – a fifty year experience of Warsaw Center of bullous diseases. *Frontiers in Immunology*, 15, 1–14.
- Mellyanawati. (2021). Laporan Kasus: Seorang anak dengan penyakit bula yang diduga Chronic Bullous Disease of Childhood A Child with Bullous Disease Suspected Chronic Bullous Disease in Childhood. *Jurnal Ilmiah Kedokteran Wijaya Kusuma*, 10(2), 176–186.
- Mori, F., Saretta, F., Liotti, L., Giovannini, M., Castagnoli, R., & Arasi, S. (2022). Linear Immunoglobulin A Bullous Dermatitis in Children. *Frontiers in Pediatrics*, 10.
- Nasri, J., Jungo, P., Blickenstorfer, M., Mühleisen, B., Navarini, A. A., & Juratli, H. A. (2022). Linear IgA bullous dermatosis of childhood. *Dermatology Online Journal*, 28(5).
- Onalaja-underwood, A. A., Hurley, M. Y., & Sokumbi, O. (2024). Diagnosis and Management of Bullous Disease. *Clinics in Geriatric Medicine*, 40, 37–74.
- Pradhan, S., Jha, K., Kumari, P., Shrestha, S., & Jha, A. K. (2022). Chronic Bullous Disease of Childhood: A Case Report and Review of Literature of Bullous Diseases in Children. *Nepal Journal of Dermatology, Venereology & Leprology*, 20(2).
- Shin, L., Li, J. T. G., & Dao, H. (2021). Updates in the Diagnosis and Management of Linear IgA Disease: A Systematic Review. *Medicina*, 57.
- Shin, S., Bai, L., & Burnett, R. T. (2021). Air pollution as a risk factor for incident chronic obstructive pulmonary disease and asthma: A 15-year population-based cohort study. *American Journal of Respiratory and Critical Care Medicine*, 203(9), 1138–1148. <https://doi.org/10.1164/rccm.201909-1744OC>
- Stoj, V., & Lu, J. (2022). Nutrition and bullous diseases. *Clinics in Dermatology*, 40(2), 156–165. <https://doi.org/10.1016/j.clindermatol.2021.10.009>
- Wilson, A., & Murrell, D. F. (2022). Clinical features of chronic bullous dermatosis of childhood. *Clinical and Experimental Dermatology*, 47, 873–881.
- Yadav, R., Poudel, I., Poudyal, Y., & Chaudhary, N. (2026). A Rare Type of Bullous Disorder in a Child. Can It Be Chronic Bullous Disease of Childhood? *Clinical Case Reports*, 14.