Review Article

Autoimmune Bullous Dermatoses in Adults: A Clinical, Histopathological, and Immunological Differential Diagnostic Approach

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International Archives of Integrated Medicine, Vol. 13, Issue 3, March, 2026.
Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 25-2-2026 **Accepted on:** 9-3-2026
Source of support: Nil **Conflict of interest:** None declared.

DOI: **10.5281/zenodo.19281060**

How to cite this article: Joshua Granados Apú, Jafeth Mora Mora, Zianny Pamela González Benavides, Karina Sandoval González, Fernando Rodríguez Flores. Autoimmune Bullous Dermatoses in Adults: A Clinical, Histopathological, and Immunological Differential Diagnostic Approach. Int. Arch. Integr. Med., 2026; 13(3): 191-203.

Abstract

Autoimmune bullous dermatoses are a heterogeneous group of rare, immune-mediated disorders characterized by blister formation affecting the skin and, in many cases, mucous membranes. These diseases arise from autoantibodies directed against specific structural proteins within the epidermis or at the dermoepidermal junction, leading to loss of tissue integrity and clinically distinct blistering patterns. The pathogenic mechanisms underlying these conditions determine their classification into intraepidermal disorders, such as pemphigus vulgaris and pemphigus foliaceus, and subepidermal disorders, including bullous pemphigoid, mucous membrane pemphigoid, linear IgA bullous dermatosis, dermatitis herpetiformis, and epidermolysis bullosa acquisita. Each entity is defined by characteristic autoantigens, immunopathological features, and clinical behavior. Accurate diagnosis

represents a major clinical challenge due to overlapping presentations and variable disease severity. A structured diagnostic approach integrating clinical evaluation, histopathological analysis, and immunological testing is therefore essential. Histopathology allows determination of the level of blister formation and inflammatory patterns, while direct immunofluorescence remains the diagnostic gold standard by demonstrating disease-specific deposition of immunoglobulins and complement components. Indirect immunofluorescence and serological assays further refine diagnosis by identifying circulating autoantibodies and their antigenic targets, supporting precise disease classification. Special clinical scenarios, including drug-induced forms, paraneoplastic associations, elderly patients with atypical presentations, and overlap syndromes, add further complexity and underscore the need for heightened diagnostic awareness. Precise diagnosis has direct therapeutic and prognostic implications, as treatment strategies and expected outcomes are closely linked to the underlying immunological profile. An integrated, multidisciplinary diagnostic framework is therefore critical for optimizing treatment selection, guiding long-term management, and improving outcomes in adults with autoimmune bullous dermatoses.

Key words

Autoimmune bullous dermatoses, pemphigus, bullous pemphigoid, immunofluorescence, histopathology, differential diagnosis.

Introduction

Autoimmune bullous dermatoses (ABD) constitute a heterogeneous group of rare, tissue-specific autoimmune diseases characterized by the development of blistering lesions affecting the skin and, frequently, the mucous membranes. These disorders arise from the production of autoantibodies directed against structural proteins located either within the epidermis or at the dermal–epidermal junction, a process that ultimately leads to loss of tissue integrity and the formation of blisters and erosions. On the basis of their clinical presentation, histopathological features, and immunological profile, ABDs are traditionally classified into several subtypes, among which pemphigus and pemphigoid diseases represent the most prevalent categories. This classification has undergone further refinement in recent years following the identification of novel target antigens, which has supported the recognition of additional disease subtypes and contributed to a more nuanced understanding of disease heterogeneity [1, 2].

From an epidemiological perspective, ABDs are considered rare disorders, although their incidence varies considerably across geographic regions and populations. Bullous pemphigoid, for example, represents the most frequently newly diagnosed ABD in Middle Franconia, Germany, highlighting regional differences in disease distribution and diagnostic recognition [2]. While these diseases predominantly affect adults, certain subtypes, including linear IgA dermatosis and epidermolysis bullosa acquisita, may also present in pediatric populations, underscoring the broad age spectrum over which autoimmune blistering diseases can occur [3, 4]. Regardless of age at onset, the chronic and often relapsing nature of ABDs imposes a substantial clinical burden, as patients frequently require prolonged or repeated therapeutic interventions to control disease activity. Without adequate management, severe complications such as extensive fluid loss, secondary infections, and systemic involvement may develop, potentially resulting in life-threatening outcomes [2].

The clinical impact of ABDs is considerable and is largely driven by the extent of skin and mucosal involvement, as well as by the propensity for scarring in specific disease entities. Conditions such as mucous membrane pemphigoid and epidermolysis bullosa acquisita are particularly associated with significant

morbidity due to chronic inflammation and fibrotic sequelae that may compromise vital functions, including vision, swallowing, or respiration [5]. Clinically, ABDs exhibit marked heterogeneity, with lesions manifesting as tense or flaccid blisters, erosions, or erythematous plaques, often in variable distributions and with differing degrees of mucosal involvement. This variability can obscure the initial clinical impression and delay diagnosis, as presentations may mimic other inflammatory, infectious, or drug-induced blistering disorders [6]. Consequently, diagnostic complexity is heightened by the overlapping clinical features among different ABD subtypes and by the requirement for specialized investigations to demonstrate disease-specific autoantibodies and characteristic histopathological patterns [4].

An integrated diagnostic approach is essential to ensure accurate classification and optimal management of autoimmune bullous dermatoses. Such an approach relies on the systematic integration of clinical assessment with histopathological examination and advanced immunological techniques, allowing for precise identification of the underlying disease mechanism [6]. Direct immunofluorescence microscopy remains the cornerstone of diagnosis, as it enables the in situ detection of tissue-bound immunoreactants and provides critical information regarding the pattern and location of antibody deposition. Complementary methods, including indirect immunofluorescence and enzyme-linked immunosorbent assays, are routinely employed to identify circulating autoantibodies and to define antigen specificity, thereby refining diagnostic accuracy [6]. Moreover, recent advances in the development of standardized serological assays targeting specific antigens, such as laminin β4 in anti-p200 pemphigoid, have further enhanced diagnostic precision and contributed to more informed therapeutic decision-making [7].

The objective of this article is to review autoimmune bullous dermatoses in adults, focusing on the clinical, histopathological, and immunological features that support an accurate and integrated differential diagnosis.

Methodology

This review on autoimmune bullous dermatoses in adults was conducted through a structured analysis of current scientific literature, with the objective of integrating clinical, histopathological, and immunological criteria relevant to differential diagnosis. The methodological approach focused on disease classification, characteristic clinical manifestations, histological patterns, and immunopathological techniques essential for accurate identification of autoimmune blistering disorders in adult patients.

The literature search was performed using PubMed, Scopus, and Web of Science, selecting peer-reviewed articles published between 2021 and 2026 in English or Spanish. Studies were included if they addressed key aspects of autoimmune bullous dermatoses, including clinical presentation, histopathology, direct and indirect immunofluorescence, serological assays, and advances in diagnostic methods. Non–peer-reviewed publications, studies with incomplete or duplicated data, or those not directly related to diagnostic evaluation were excluded. The search strategy was guided by the following keywords: *Autoimmune bullous dermatoses, pemphigus, bullous pemphigoid, immunofluorescence, histopathology, differential diagnosis.*

All selected publications were critically analyzed using a qualitative and integrative approach to extract and synthesize information on diagnostic criteria, distinguishing features among disease subtypes, and the strengths and limitations of available diagnostic tools. Artificial intelligence tools were used as complementary resources to support thematic organization and conceptual linkage of clinical, histological, and immunological data. This methodological framework enabled the development of a coherent and concise synthesis of current

evidence, emphasizing the value of an integrated diagnostic strategy for improving diagnostic accuracy and clinical decision-making in adults with suspected autoimmune bullous dermatoses.

Pathophysiological and Immunological Basis

The skin is composed of multiple layers, with the epidermis forming the outermost barrier and the dermis providing structural and functional support beneath it. The interface between these two compartments, known as the dermoepidermal junction (DEJ), plays a fundamental role in maintaining skin integrity by anchoring the epidermis to the underlying dermis. In autoimmune bullous dermatoses, the DEJ represents a key anatomical target, as it is frequently the site of immune-mediated injury that culminates in blister formation. A representative example is epidermolysis bullosa acquisita, in which autoantibodies are directed against type VII collagen, a major structural component of anchoring fibrils within the DEJ, resulting in loss of adhesion and the development of subepidermal blisters [8].

The pathogenic process in autoimmune bullous dermatoses is driven by the immune recognition of specific structural proteins that function as autoantigens. In pemphigus vulgaris, desmogleins 1 and 3 are the primary targets of pathogenic autoantibodies, and their disruption compromises desmosomal adhesion between keratinocytes, leading to intraepidermal blistering [9]. In contrast, bullous pemphigoid is characterized by autoantibodies directed against BP180, also known as type XVII collagen, and BP230, both of which are integral components of hemidesmosomes that anchor the epidermis to the basement membrane. The immune attack on these structures results in separation at the dermoepidermal junction and the formation of subepidermal blisters [10, 11]. Similarly, in epidermolysis bullosa acquisita, type VII collagen serves as the principal autoantigen, reinforcing the role of DEJ components in subepidermal blistering disorders [8].

Autoantibody production in autoimmune bullous dermatoses is primarily mediated by B lymphocytes, although the pathogenic process is modulated by the coordinated involvement of T cells and other immune effector cells, which collectively contribute to immune dysregulation and disease progression [12]. In bullous pemphigoid, circulating autoantibodies can be detected prior to the appearance of clinical symptoms, suggesting the existence of a preclinical phase characterized by subclinical immune activation and loss of tolerance [11]. Once autoantibodies are present, they can initiate downstream inflammatory processes through activation of the complement system, thereby amplifying tissue injury. In bullous pemphigoid, complement activation is associated with a MyD88-dependent proinflammatory response in keratinocytes, which plays a central role in disease pathogenesis [13]. This inflammatory milieu promotes the recruitment of effector cells, including eosinophils and mast cells, further intensifying inflammation and contributing directly to blister formation [12].

The clinical and histopathological differences between intraepidermal and subepidermal blistering disorders reflect distinct pathogenic mechanisms. Intraepidermal blistering, as observed in pemphigus vulgaris, arises from autoantibody-mediated disruption of desmosomes, leading to acantholysis and blister formation within the epidermal layer [9]. In contrast, subepidermal blistering, which characterizes conditions such as bullous pemphigoid and epidermolysis bullosa acquisita, results from immune-mediated damage to structural components of the dermoepidermal junction, producing a plane of cleavage between the epidermis and dermis [8, 10].

Clinical Classification of Autoimmune Bullous Dermatoses

Intraepidermal bullous diseases are defined by the formation of blisters within the epidermis as a consequence of autoantibody-mediated disruption of intercellular adhesion. Among these

disorders, pemphigus vulgaris represents the most frequent and clinically significant entity. Pemphigus vulgaris is characterized by the presence of pathogenic autoantibodies directed primarily against desmoglein 3 and, in some cases, desmoglein 1, resulting in loss of keratinocyte cohesion and blistering of the skin and mucous membranes [14]. Histopathologically, the disease is marked by suprabasal acantholysis, a finding that reflects the cleavage plane above the basal layer and constitutes a hallmark of the condition. Immunologically, the detection of IgG autoantibodies is a central diagnostic feature. Clinically, pemphigus vulgaris often involves both cutaneous and mucosal surfaces; however, disease expression is heterogeneous, and some patients may present predominantly with skin lesions in the absence of significant mucosal involvement [15, 16].

Pemphigus foliaceus represents another intraepidermal blistering disorder within the pemphigus spectrum and is distinguished by its immunological and clinical profile. This condition is associated with autoantibodies targeting desmoglein 1, which is predominantly expressed in the superficial layers of the epidermis, thereby explaining the characteristic superficial blistering observed in affected patients [15]. Unlike pemphigus vulgaris, pemphigus foliaceus does not involve mucosal surfaces, reflecting the limited expression of desmoglein 1 in mucosal epithelium. Clinically, the disease course is generally less severe, as the blistering process remains confined to the upper epidermal layers and does not compromise deeper structural integrity [17].

Paraneoplastic pemphigus constitutes a distinct and particularly severe form of intraepidermal bullous disease, characterized by its association with underlying neoplastic conditions. The immunopathogenesis of paraneoplastic pemphigus involves autoantibodies directed not only against desmoglein 3 but also against members of the plakin family, reflecting a broader spectrum of antigenic targets. Clinically, this disorder is notable for its extensive and often refractory mucosal involvement, which may precede or accompany cutaneous manifestations. The strong association with malignancies and the severity of mucocutaneous disease contribute to a high risk of morbidity and mortality, rendering paraneoplastic pemphigus a potentially life-threatening condition [18].

In contrast to intraepidermal disorders, subepidermal bullous diseases are characterized by blister formation beneath the epidermis, resulting from immune-mediated injury to components of the basement membrane zone. Bullous pemphigoid is the most common of these conditions and is defined by the presence of autoantibodies directed against hemidesmosomal proteins, leading to separation at the dermoepidermal junction and the formation of subepidermal blisters. Clinically, bullous pemphigoid typically presents with tense blisters on erythematous or normal-appearing skin and predominantly affects elderly individuals, reflecting both immunosenescence and age-related changes in skin structure [1].

Mucous membrane pemphigoid represents a related subepidermal blistering disorder in which mucosal involvement predominates. This disease is associated with autoantibodies targeting various components of the basement membrane zone, resulting in chronic inflammation and blistering primarily affecting mucosal surfaces. A defining clinical feature of mucous membrane pemphigoid is its propensity to cause scarring, which can lead to significant and irreversible morbidity, particularly when the eyes, oral cavity, or upper aerodigestive tract are involved [1, 2].

Linear IgA bullous dermatosis is another subepidermal autoimmune blistering disease distinguished by the linear deposition of IgA along the basement membrane zone. Clinically, it may resemble bullous pemphigoid, with blistering of the skin, but it can also involve

mucous membranes, contributing to diagnostic complexity. Immunopathologically, the presence of linear IgA deposits is a defining feature and serves as a critical criterion for differentiation from other subepidermal entities [1].

Dermatitis herpetiformis is a subepidermal blistering disorder strongly associated with gluten sensitivity. It is characterized by intensely pruritic vesicles and papules, most commonly distributed on extensor surfaces, and reflects an underlying immune response linked to dietary antigens. The disease is immunologically defined by granular IgA deposits within the dermal papillae, a finding that underpins both diagnosis and pathogenesis [1, 14].

Epidermolysis bullosa acquisita is a further example of a subepidermal bullous disease and is characterized by autoantibodies directed against type VII collagen, a key structural component of anchoring fibrils at the dermoepidermal junction. Clinically, the disease may mimic other subepidermal blistering disorders, which can complicate diagnosis. However, its specific autoantigen target and tendency toward scarring provide important distinguishing features that support accurate classification within the spectrum of autoimmune bullous dermatoses [1, 14].

Histopathological Evaluation

Accurate histopathological evaluation of autoimmune bullous dermatoses relies heavily on appropriate biopsy techniques and careful selection of sampling sites. For optimal diagnostic yield, biopsies should be obtained from the edge of a fresh blister or from erythematous skin immediately adjacent to a blister, as this approach allows simultaneous assessment of the blister cavity and the surrounding tissue architecture. This strategy provides a comprehensive view of the pathological process and increases the likelihood of identifying diagnostic features. In clinical practice, punch biopsy is the technique most commonly employed, and particular attention must be given to ensuring that the specimen includes the dermoepidermal junction, which is essential for the evaluation of subepidermal blistering disorders [19].

On light microscopy, intraepidermal blistering disorders are characterized by distinctive histological features that reflect the underlying loss of intercellular adhesion. Acantholysis, defined by the separation of keratinocytes, is a hallmark finding and results in blister formation within the epidermis, as typically observed in pemphigus vulgaris. This pattern is clearly distinguishable from subepidermal blistering diseases such as bullous pemphigoid. Additional histological findings may include eosinophilic spongiosis and acantholytic dermatitis, both of which support the diagnosis of intraepidermal blistering and contribute to the differentiation from other inflammatory dermatoses [20].

In contrast, subepidermal blistering disorders display a different histopathological architecture. In bullous pemphigoid, light microscopy typically reveals a subepidermal blister accompanied by a mixed inflammatory infiltrate located beneath the epidermis, composed predominantly of eosinophils and neutrophils [12, 21]. The inflammatory profile can be further characterized using direct immunofluorescence, which frequently demonstrates linear deposits of IgG and complement component C3 along the basement membrane zone, a finding that is highly characteristic of bullous pemphigoid and supports the histological diagnosis [22].

The composition of the inflammatory infiltrate provides additional diagnostic and pathogenic insights. Eosinophils play a prominent role in bullous pemphigoid and are commonly identified within the blister cavity and the surrounding dermal tissue, where they contribute to tissue injury and amplification of the inflammatory response [21]. Neutrophils are also present and participate in the acute inflammatory process, while lymphocytes contribute to the adaptive immune response underlying disease chronicity

[12]. This inflammatory environment is further shaped by the release of cytokines, including interleukin-6 and interleukin-24, which are involved in sustaining the proinflammatory cascade characteristic of bullous pemphigoid [13].

Despite its central role in diagnosis, routine histopathology has inherent limitations and potential pitfalls. In some cases, histological findings may be non-specific, making it difficult to reliably distinguish between different autoimmune bullous diseases without the support of immunofluorescence studies [23]. In addition, improper biopsy site selection can result in samples that fail to capture the defining pathological features of the disease, thereby increasing the risk of misdiagnosis [19]. Furthermore, the histological appearance of bullous pemphigoid may overlap with that of other inflammatory dermatoses, reinforcing the need for careful correlation of histopathological findings with clinical presentation and immunological data to achieve an accurate and definitive diagnosis [22].

Immunopathological and Immunological Studies

Direct immunofluorescence is a cornerstone in the diagnostic evaluation of autoimmune bullous dermatoses, as it allows for the detection of tissue-bound autoantibodies within affected skin. The technique is performed on a perilesional skin biopsy and involves the application of fluorescein-labeled antibodies to visualize deposits of immunoglobulins and complement components within the tissue [6]. Through this methodology, characteristic deposition patterns can be identified, which are essential for disease classification. Direct immunofluorescence commonly demonstrates linear or granular patterns of immunoreactant deposition. For example, linear IgA bullous dermatosis is defined by the presence of linear IgA deposits along the basement membrane zone, a finding that is highly specific and diagnostically informative [4, 18]. The diagnostic significance of direct immunofluorescence lies in the identification of immunoglobulin classes and complement components, including IgG, IgA, IgM, and C3, in distinct distribution patterns. Linear deposition of IgG and C3, for instance, is observed in conditions such as bullous systemic lupus erythematosus and epidermolysis bullosa acquisita, whereas predominant IgA deposition is characteristic of linear IgA bullous dermatosis [4, 24].

Indirect immunofluorescence complements direct immunofluorescence by enabling the detection of circulating autoantibodies in patient serum. This technique involves incubating patient serum with an appropriate substrate, most commonly normal human skin, to assess antibody binding patterns that reflect underlying disease processes [6]. A particularly valuable variation of this method is the salt-split skin technique, which induces cleavage at the dermal–epidermal junction and allows for precise localization of autoantibody binding. This approach is instrumental in differentiating between subepidermal bullous diseases, as autoantibodies in epidermolysis bullosa acquisita bind to the dermal side of the split, whereas those in bullous pemphigoid bind to the epidermal side [25]. The correlation between indirect immunofluorescence findings and specific disease subtypes enhances diagnostic accuracy, and additional analyses, such as IgG subclass determination, can further aid in distinguishing closely related conditions, including bullous systemic lupus erythematosus and epidermolysis bullosa acquisita [24].

Serological and molecular assays provide further refinement of the diagnostic process by enabling precise identification of disease-specific autoantibodies and their target antigens. Enzyme-linked immunosorbent assay is widely used to detect circulating autoantibodies against defined antigens, such as BP180 in bullous pemphigoid, and offers high sensitivity and reproducibility in routine clinical practice. Complementary techniques, including immunoblotting and immunoprecipitation, allow for detailed

characterization of autoantigen specificity and are particularly useful in identifying less common antibody profiles, such as IgA autoantibodies directed against BP180 in linear IgA bullous dermatosis. In parallel, emerging biomarkers and advanced diagnostic tools, including fluorescence overlay antigen mapping and direct immunoelectron microscopy, are being developed to enhance diagnostic precision and to facilitate differentiation between closely related autoimmune bullous diseases [4, 6, 26].

Integrated Differential Diagnostic Algorithm

The diagnostic evaluation of autoimmune bullous dermatoses follows a stepwise strategy that integrates clinical, histological, and immunological assessments to achieve accurate disease classification. The process begins with a thorough clinical evaluation aimed at identifying characteristic blisters, erosions, and their distribution on the skin and mucosal surfaces. Clinical presentation is highly variable and may include erythematous, urticarial, or eczematous lesions, which can obscure the initial diagnosis and necessitate further investigation [6].

Histological examination represents a pivotal component of this diagnostic sequence. Skin biopsy is indispensable, as it allows for evaluation of the level of blister formation and associated inflammatory patterns. In particular, direct immunofluorescence microscopy performed on a perilesional biopsy remains the diagnostic gold standard for autoimmune bullous dermatoses, as it reveals disease-specific patterns of immunoglobulin and complement deposition within the skin [6, 27]. Histopathological findings must then be interpreted in conjunction with immunopathological data, as morphology alone is often insufficient to distinguish between closely related entities. Immunological testing further refines the diagnosis through the detection of circulating autoantibodies using enzyme-linked immunosorbent assay or indirect immunofluorescence microscopy. These techniques enable identification of autoantigen-specific antibodies, such as desmoglein 1 and 3 in pemphigus, BP180 in bullous pemphigoid, and laminin 332 in mucous membrane pemphigoid, thereby supporting precise disease classification [1, 6].

Within this integrated framework, recognition of key distinguishing features is essential for differential diagnosis. Pemphigus disorders are defined by intraepithelial blister formation resulting from autoantibodies directed against desmogleins, whereas pemphigoid diseases are characterized by subepidermal blistering associated with antibodies targeting components of the basement membrane zone [1, 28]. Linear IgA bullous dermatosis is differentiated by the presence of linear IgA deposition along the basement membrane, a finding that is often associated with systemic conditions such as inflammatory bowel disease and provides a clear immunopathological signature [4, 27]. Anti-p200 pemphigoid represents a further diagnostic challenge, as its clinical features may closely resemble those of bullous pemphigoid; however, it is distinguished by autoantibodies directed against a 200 kDa protein located at the dermal–epidermal junction [7].

To support clinical decision-making, diagnostic flowcharts and practical algorithms have been developed to systematically guide clinicians from initial presentation to definitive diagnosis. These tools provide a structured pathway that integrates clinical findings with histological and immunological results, facilitating exclusion of alternative diagnoses and confirmation of autoimmune bullous dermatoses [3, 24]. Practical algorithms further emphasize the importance of correlating clinical manifestations with laboratory data, reinforcing the need for a comprehensive and methodical approach to diagnosis in order to ensure accuracy and optimize patient management [4, 6].

Special Clinical Scenarios in Adults

Drug-induced autoimmune bullous dermatoses represent a clinically relevant subset of blistering disorders in which medications act as triggers of immune dysregulation. Linear IgA bullous dermatosis and bullous pemphigoid are the most frequently reported drug-induced entities. Linear IgA bullous dermatosis has been associated with antibiotics such as vancomycin and amoxicillin, as well as with nonsteroidal anti-inflammatory drugs and cardiovascular agents, reflecting the broad spectrum of drugs implicated in its pathogenesis [29]. Bullous pemphigoid, in contrast, is commonly linked to dipeptidyl peptidase 4 inhibitors and antineoplastic immunotherapies, which may promote immune activation and proteolytic damage to basement membrane components [30].

Paraneoplastic associations constitute another important diagnostic consideration. Paraneoplastic autoimmune multiorgan syndrome, also known as paraneoplastic pemphigus, is strongly associated with underlying neoplasms, particularly lymphoproliferative disorders, and is characterized by severe mucositis and polymorphic cutaneous lesions. Early recognition is essential, as diagnosis directly impacts the management of both the autoimmune dermatosis and the associated malignancy [30].

Elderly patients are especially susceptible to drug-induced linear IgA bullous dermatosis, with a high proportion of cases reported in individuals between 66 and 85 years of age. In this population, atypical clinical presentations are common and may delay diagnosis, underscoring the need for careful clinical assessment and heightened diagnostic suspicion [29]. Overlap syndromes further highlight disease complexity, as linear IgA bullous dermatosis may coexist with inflammatory bowel disease, and improvement in cutaneous manifestations has been observed following control of intestinal disease activity, reinforcing the importance of an integrated clinical approach [27].

Therapeutic Implications of Accurate Diagnosis

Accurate diagnosis plays a central role in guiding treatment selection in autoimmune bullous dermatoses, as it allows therapies to be tailored to the specific disease entity and its underlying pathogenic mechanisms. In bullous pemphigoid, precise identification of the disorder supports the use of systemic glucocorticoids for rapid control of inflammation and blistering, while enabling the early introduction of adjunctive immunosuppressive agents to reduce cumulative steroid exposure and limit long-term adverse effects [28. Similarly, in mucous membrane pemphigoid, an accurate diagnosis permits the selection of disease-specific therapies, such as dapsone or cyclophosphamide, with treatment choices guided by the severity of involvement and the anatomic sites affected [5]. In linear IgA dermatosis, diagnostic confirmation directs the use of agents such as dapsone and systemic corticosteroids, with therapeutic strategies adapted to the individual patient's immunological profile and clinical course [3].

Disease-specific therapeutic strategies further underscore the importance of diagnostic precision. Management of bullous pemphigoid commonly relies on systemic corticosteroids combined with immunosuppressive therapies, while emerging treatments targeting key pro-inflammatory mediators have demonstrated potential benefits in refractory disease [32]. In mucous membrane pemphigoid, biologic agents such as rituximab have shown efficacy in achieving disease control and symptom resolution in a substantial proportion of patients, particularly in severe or treatment-resistant cases [5]. Treatment of linear IgA dermatosis is largely guided by expert consensus, emphasizing individualized therapeutic planning based on disease severity, distribution, and response to initial interventions [3].

Beyond immediate treatment decisions, immunological profiles carry important prognostic implications. The presence and

specificity of circulating autoantibodies can influence both disease course and therapeutic response. In bullous pemphigoid, for example, autoantibodies directed against BP180 and BP230 have been associated with distinct clinical patterns and responses to therapy, providing valuable prognostic information [32]. A comprehensive understanding of the immunological mechanisms underlying autoimmune bullous dermatoses therefore contributes not only to accurate diagnosis and targeted treatment selection but also to the anticipation of disease evolution and the development of effective long-term management strategies [19].

Conclusions

Autoimmune bullous dermatoses comprise a heterogeneous group of disorders whose pathogenesis is determined by autoantibody-mediated targeting of specific structural proteins within the epidermis or at the dermoepidermal junction, resulting in distinct intraepidermal or subepidermal blistering patterns. Understanding these pathophysiological and immunological mechanisms is essential for accurate disease classification and for explaining the clinical and histopathological diversity observed across different entities.

Accurate diagnosis of autoimmune bullous dermatoses relies on an integrated approach that combines careful clinical evaluation with histopathological examination and advanced immunopathological techniques, particularly direct and indirect immunofluorescence and serological assays. This stepwise diagnostic strategy is critical for distinguishing between closely related diseases, avoiding misdiagnosis, and addressing diagnostic challenges arising from overlapping clinical or histological features.

Precise identification of the specific autoimmune bullous disease has direct therapeutic and prognostic implications, as treatment selection and expected outcomes are closely linked to the underlying immunological profile. A comprehensive diagnostic framework therefore not only improves diagnostic accuracy but also supports individualized treatment strategies and informed long-term management, ultimately contributing to improved patient outcomes.

References

1. Hashimoto T, Qian H, Ishii N, Nakama T, Tateishi C, Tsuruta D, et al. Classification and antigen molecules of autoimmune bullous diseases. Biomolecules [Internet]. 2023 Apr 20;13(4):703. Available from: https://doi.org/10.3390/biom13040703
2. Sollfrank L, Schönfelder V, Sticherling M. Retrospective analysis of autoimmune bullous diseases in Middle Franconia. Frontiers in Immunology [Internet]. 2023 Oct 10;14:1256617. Available from: https://doi.org/10.3389/fimmu.2023.1256617
3. Caux F, Patsatsi A, Karakioulaki M, Antiga E, Baselga E, Borradori L, et al. 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 [Internet]. 2024 Feb 29;38(6):1006–23. Available from: https://doi.org/10.1111/jdv.19880
4. Kowalewski C, Wozniak K. Linear IgA bullous dermatosis–a fifty year experience of Warsaw Center of bullous diseases. Frontiers in Immunology [Internet]. 2025 Jan 14;15:1478318. Available from: https://doi.org/10.3389/fimmu.2024.1478318
5. Sprague K, Sivesind T, Szeto M, Dellavalle R, Kirtschig G. From the Cochrane Library: Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. Journal of the American Academy of

Dermatology [Internet]. 2022 Feb 14;86(6):e273–4. Available from: https://doi.org/10.1016/j.jaad.2022.02.017

6. Van Beek N, Holtsche MM, Atefi I, Olbrich H, Schmitz MJ, Pruessmann J, et al. State-of-the-art diagnosis of autoimmune blistering diseases. Frontiers in Immunology [Internet]. 2024 Jun 6;15:1363032. Available from: https://doi.org/10.3389/fimmu.2024.1363032
7. Kasperkiewicz M, Pigors M, Holtsche MM, Goletz S, Schmidt E. Anti-p200 pemphigoid. British Journal of Dermatology [Internet]. 2025 Aug 23;194(1):10–7. Available from: https://doi.org/10.1093/bjd/ljaf324
8. Perković D, Mokos Z, Marinović B. Epidermolysis Bullosa Acquisita—Current and emerging treatments. Journal of Clinical Medicine [Internet]. 2023 Feb 1;12(3):1139. Available from: https://doi.org/10.3390/jcm12031139
9. Egu D, Schmitt T, Waschke J. Mechanisms Causing Acantholysis in Pemphigus-Lessons from Human Skin. Frontiers in Immunology [Internet]. 2022 May 16;13:884067. Available from: https://doi.org/10.3389/fimmu.2022.884067
10. Cole C, Borradori L, Amber KT. Deciphering the contribution of BP230 autoantibodies in bullous pemphigoid. Antibodies [Internet]. 2022 Jun 28;11(3):44. Available from: https://doi.org/10.3390/antib11030044
11. Mai Y, Izumi K, Mai S, Ujiie H. The significance of preclinical anti-BP180 autoantibodies. Frontiers in Immunology [Internet]. 2022 Aug 8;13:963401. Available from: https://doi.org/10.3389/fimmu.2022.963401
12. Yan T, Zhang Z. Adaptive and innate immune pathogenesis of bullous pemphigoid: A review. Frontiers in Immunology [Internet]. 2023 Mar 10;14:1144429. Available from: https://doi.org/10.3389/fimmu.2023.1144429
13. Bao L, Guerrero-Juarez CF, Li J, Pigors M, Emtenani S, Liu Y, et al. IgG autoantibodies in bullous pemphigoid induce a pathogenic MyD88-dependent pro-inflammatory response in keratinocytes. Nature Communications [Internet]. 2025 Aug 6;16(1):7254. Available from: https://doi.org/10.1038/s41467-025-62495-2
14. Didona D, Scarsella L, Hudemann C, Volkmann K, Zimmer CL, Beckert B, et al. Type 2 T-Cell Responses against Distinct Epitopes of the Desmoglein 3 Ectodomain in Pemphigus Vulgaris. Journal of Investigative Dermatology [Internet]. 2023 Sep 15;144(2):263-272.e8. Available from: https://doi.org/10.1016/j.jid.2023.07.025
15. Terada A, Akasaka E, Nakano H, Sawamura D. Two cases of cutaneous-type pemphigus vulgaris and a case of pemphigus foliaceus without mucosal involvement despite high anti-desmoglein 3 autoantibody levels. The Journal of Dermatology [Internet]. 2023 Jul 23;50(11):1501–5. Available from: http://dx.doi.org/10.1111/1346-8138.16907
16. Ramos R, Cepero C, Rivera P, Ruiz H, Martin J. S2678 Don't forget the pemphigus! The American Journal of Gastroenterology [Internet]. 2023 Oct 1;118(10S):S1836. Available from: http://dx.doi.org/10.14309/01.ajg.0000960352.06073.d5
17. Montagnon C, Tolkachjov SN, Murrell DF, Camilleri MJ, Lehman JS. Intraepithelial autoimmune blistering dermatoses: Clinical features and diagnosis. Journal of the American Academy of Dermatology [Internet]. 2021 Mar 5;84(6):1507–19. Available

from: https://doi.org/10.1016/j.jaad.2020.11.075

18. Wang X, Wang R, Bu D, Wang L, Zhang Y, Chang Y, et al. Paraneoplastic pemphigus autoantibodies against C-terminus of desmoplakin induced acantholysis in vitro and in vivo. Frontiers in Immunology [Internet]. 2022 Jul 14;13:886226. Available from: https://doi.org/10.3389/fimmu.2022.886226
19. Borradori L, Van Beek N, Feliciani C, Tedbirt B, Antiga E, Bergman R, et al. UpdatedS2K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). Journal of the European Academy of Dermatology and Venereology [Internet]. 2022 Jun 29;36(10):1689–704. Available from: https://doi.org/10.1111/jdv.18220
20. Gonzalez A, Maiberger M. 42357 Bullous pemphigoid presenting as erythema multiforme-like targetoid lesions. Journal of the American Academy of Dermatology [Internet]. 2023 Sep 1;89(3):AB131. Available from: https://doi.org/10.1016/j.jaad.2023.07.525
21. Limberg M, Weihrauch T, Gray N, Ernst N, Hartmann K, Raap U. Eosinophils, basophils, and neutrophils in bullous pemphigoid. Biomolecules [Internet]. 2023 Jun 21;13(7):1019. Available from: https://doi.org/10.3390/biom13071019
22. Janela R, Ishii N, Castel M, Jouen F, Cellier L, Courville P, et al. Mixed muco-cutaneous pemphigoid: Clinical and immunological features of 15 cases. Frontiers in Immunology [Internet]. 2023 Mar 15;14:1134720. Available from: https://doi.org/10.3389/fimmu.2023.1134720
23. Nieto L, Suárez R. Unmet needs in bullous pemphigoid: definition of accurate and combined diagnostic criteria. Journal of the European Academy of Dermatology and Venereology [Internet]. 2022 Jan 16;36(5):e394–6. Available from: https://doi.org/10.1111/jdv.17935
24. Khosravi T, Crawford R, Wong A, Dutz J. 44274 Direct immunofluorescence IgG autoantibody subclass analysis as a tool to differentiate between bullous systemic lupus erythematosus and epidermolysis bullosa acquisita. Journal of the American Academy of Dermatology [Internet]. 2023 Sep 1;89(3):AB37. Available from: https://doi.org/10.1016/j.jaad.2023.07.151
25. Minakawa S, Matsuzaki Y, Yao S, Sagara C, Akasaka E, Koga H, et al. Case report: A case of epidermolysis bullosa acquisita with IgG and IgM anti-basement membrane zone antibodies relapsed after COVID-19 mRNA vaccination. Frontiers in Medicine [Internet]. 2023 May 30;10:1093827. Available from: https://doi.org/10.3389/fmed.2023.1093827
26. Zhou Y, Zhou X, Feng X, Xia D, Qian H, Liu H, et al. Case Report: Prurigo nodularis-like linear IgA/IgG bullous dermatosis: a case report and literature review. Frontiers in Immunology [Internet]. 2023 May 30;14:1201163. Available from: http://dx.doi.org/10.3389/fimmu.2023.1201163
27. Weng P, Hung Y, Le P, Huang Y. Linear IGA bullous dermatosis in association with Crohn disease. Mayo Clinic Proceedings [Internet]. 2022 Nov 1;97(11):1969–70. Available from: https://doi.org/10.1016/j.mayocp.2022.06.038

28. Chu K, Yu H, Yu S. Current and Innovated Managements for Autoimmune bullous Skin Disorders: An Overview. Journal of Clinical Medicine [Internet]. 2022 Jun 19;11(12):3528. Available from: https://doi.org/10.3390/jcm11123528
29. Yang Y, Xie H, Liu S, Jia Y, Cui B, Xiao Z. Linear IgA bullous dermatosis secondary to drugs: a real-world pharmacovigilance study of the FDA adverse event reporting system. Frontiers in Medicine [Internet]. 2025 Jan 23;12:1521697. Available from: https://doi.org/10.3389/fmed.2025.1521697
30. De Nicolas B, Ballester A, Garcia E, Berna E, Azcarraga C, Fernandez M. From molecular insights to clinical perspectives in Drug-Associated Bullous Pemphigoid. International Journal of Molecular Sciences [Internet]. 2023 Nov 26;24(23):16786. Available from: https://doi.org/10.3390/ijms242316786
31. Alpsoy E. Paraneoplastic autoimmune multiorgan syndrome (paraneoplastic pemphigus): How and why should we recognize atypical cases early? Journal of the European Academy of Dermatology and Venereology [Internet]. 2022 Dec 14;37(1):14–5. Available from: https://doi.org/10.1111/jdv.18724
D'Agostino G, Rizzetto G, Marani A, Marasca S, Candelora M, Gambini D, et al. Bullous pemphygoid and novel therapeutic approaches. Biomedicines [Internet]. 2022 Nov 8;10(11):2844. Available from: https://doi.org/10.3390/biomedicines10112844