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Review on Bullous Pemphigoid: Fixed Drug Eruption or Autoimmune Disorder

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ABSTRACT

Background: Bullous pemphigoid is a blistering disease of autoimmune nature predominantly affecting the geriatric population. It is characterized by blister formation at the subepidermal level, due to autoantibodies at the dermo-epidermal junction targeting proteins BP180XV11 and BP230. Mainly an autoimmune condition, diagnosis and treatment get complicated as it overlaps with drug-induced hypersensitivity reactions, including fixed drug eruption. Unlike Bullous Pemphigoid, it is a condition of localized hypersensitivity mediated by T cells.

Purpose: The review tries to establish Bullous Pemphigoid as an autoimmune condition separate from fixed drug eruption. It is centered on the causative role of medications, which include diuretics, antibiotics, and dipeptidyl peptidase-4 inhibitors, in drug-induced bullous pemphigoid. Besides, it examines genetic, immunological, and environmental etiologies of the disease and delineates clinical and diagnostic characteristics of Bullous Pemphigoid and fixed drug eruptions.

Method: A systematic analysis of current literature was performed, focusing on the pathophysiology, immunological mechanisms, and histopathological differences between Bullous Pemphigoid and fixed drug eruptions. The review also examines the role of medications, genetic predispositions such as specific human leukocyte antigen haplotypes, and the diagnostic utility of histopathological and immunological methods like direct immunofluorescence.

Results: Autoantibodies against BP180 and BP230 in bullous pemphigoid initiate inflammatory cascades, causing subepidermal blistering and eosinophilic infiltration. Fixed drug eruption involves basal cell necrosis and localized lymphocytic infiltration. Drugs like dipeptidyl peptidase-4 inhibitors exacerbate bullous pemphigoid through immune modulation and oxidative stress. Genetic susceptibility plays a significant role, and immunological tests such as direct immunofluorescence help distinguish the two conditions.

Conclusion: Bullous pemphigoid is a distinct autoimmune disease with unique immunopathological mechanisms compared to fixed drug eruption. Understanding its pathogenesis, drug interactions, and diagnostic methods enhances accurate diagnosis and management of both spontaneous and drug-induced bullous pemphigoid.

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1. Introduction

Bullous is a medical term that refers to a large blister characterized by the presence of a thin-walled sac with clear liquid. Pemphigoid refers to a prototypical blistering skin autoimmune disease that is mediated by Type II hypersensitivity with anti-hemidesmosome antibody formation (Holgate *et al.*, 2009). It is clinically presented as the formation of tense bullae filled with serous or hemorrhagic fluid on an erythematous or urticarial base. The most common type is "Bullous Pemphigoid" (BP), i.e., a subepidermal blistering with inflammation formed due to fluid accumulation in between the epidermal cells and basal membrane, resulting in blister formation. The disease is accompanied by intense pruritus, significantly impacting the quality of life. Generally, these blisters are not visible at the very initial stage but they can be identified by purple to

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red lessons in the chest, stomach, thigh, inner parts of the limbs, and back region, apart from these blisters may occur in the arm and leg region. 20% of patients with classical BP suffer from non-specific itchy lesions in the non-bullous stage at the onset of the disease (Nanda *et al.*, 2004).

The epidemiology of BP highlights its rising incidence, especially in aging populations globally, being 2.4-23 cases/ million in common populations per year; also, it raises exponentially in more than 80-year-old individuals. It affects both elderly males and females equally with an average onset of 75 years.

BP is also recorded in children in many countries, including India. Although the etiology of the illness can be triggered by drugs, the causal factor is usually unknown (Langan *et al.*, 2008). It is mostly brought on by the oral and occasionally topical use of certain medications. An alternative name for this variation is Drug-Induced Bullous Pemphigoid (DIBP).

2. Fixed Drug Eruption (FDE)

This was named for its defining feature because of fixed lesion recurrence at the same site upon subsequent exposures to the causative drug lesions that recur between 0.5 hours to 8 hours**,** typically at the same site. Severity may increase with repeated exposures (Baican *et al.*, 2010). FDE typically targets areas such as lips, feet, face, hands, and genitalia; mucosal involvement is also frequent. This is often associated with pain, annoying lesions, and pruritus.

FDE can be mistaken for other dermatological conditions that include erythema multiforme (characterized by target lesions with a lack of fixed recurrence), Steven Johnson syndrome (identified by systemic symptoms and widespread epidermal detachment), and bullous pemphigoid. FDE represents a type IV hypersensitivity reaction, mediated primarily via drug-specific memory T cells localized in the skin (Alpsoy *et al.*, 2015). FDE may occur by any age, frequently reported more in adults, the period prevalence varies based on the drug usage patterns, and prescribing practices, with higher rate in areas where medications like NSAIDs (Ibuprofen, naproxen, diclofenac), antimicrobials (tetracycline, sulphonamides) others like paracetamol, allopurinol etc are used commonly. Bullous Fixed Drug Eruption (Bullous FDE) is considered rare, primarily because it occurs only as a specific reaction to certain medications, rather than as a broad autoimmune response (Taquin *et al.*, 2016).

In Bullous FDE, blisters form in response to a particular drug, and these lesions reappear in the same locations upon re-exposure to the triggering medication. This condition is distinct from Bullous Pemphigoid (BP), which is more generalized and chronic, involving a systemic autoimmune attack on skin proteins without a direct drug trigger in most cases (Schmidt & Zillikens, 2013). The rarity of Bullous FDE underscores the argument that BP is predominantly an autoimmune disorder, as BP involves a widespread immune system malfunction where the body erroneously targets its own skin proteins (BPAG1 and BPAG2) (Ujiie *et al.*, 2011).

This autoimmune mechanism in BP leads to the characteristic chronic blistering, distinguishing it from the more localized and drug-specific nature of Bullous FDE. The comparison highlights BP's basis in systemic autoimmunity rather than isolated drug hypersensitivity (Kershenovich *et al.*, 2014). In the early stages, when the memory CD8+ T-cells are activated by the drug antigen, the epidermal basal layer is damaged due to the release of interferon-gamma at the dermo-epidermal junction.

After drug discontinuation, the basal layer of the epidermis starts regenerating by undergoing cell apoptosis, and the basal layer releases interleukin-15 (IL-15) during regeneration that results in the formation of memory CD8+ T-cells in the same site of fixed drug eruption occurrence. Over 100 medications are responsible for FDE; among these, FDE is commonly seen with NSAIDs, co-trimoxazole, fluoroquinolones, nitroimidazoles, etc. (Verheyden *et al.*, 2020).

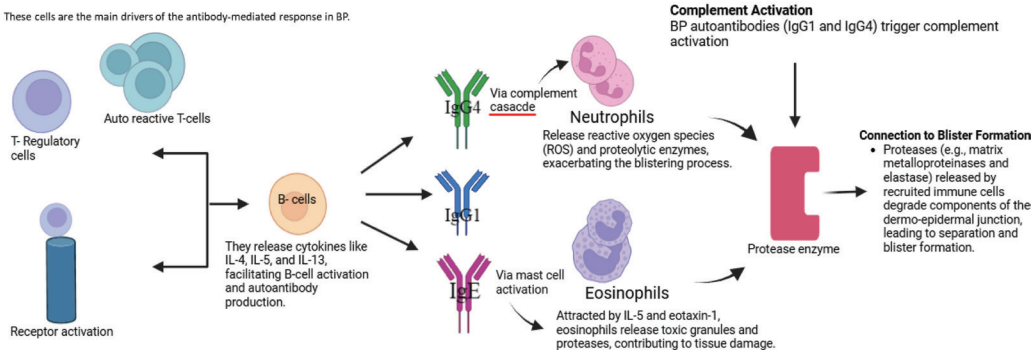

Figure 1: Immunological Mechanism of Bullous Pemphigoid (BP)

BP is a chronic autoimmune blistering disease where autoantibodies predominantly cause subepidermal blisters due to involvement with the hemidesmosomal proteins BP180, collagen XVII, and BP230. T cells are essential for BP autoimmune response regulation. Cytokines are signaling proteins that modulate immunological reactions. Some of the examples of particular cytokines are Th2 cytokines and Th17 cells. These cells cause an attraction of neutrophils by IL-17 and IL-23 and lead to increased inflammation and tissue damage. Th2 cytokines play a crucial role in BP because the disease manifests with a Th2-shifted immune response. They evoke the production of IL-4 and IL-13. These, in turn, cause B-cell activation and initiate the production of IgG autoantibodies for BP180 and BP230. IL-5 further leads the recruitment and activation of eosinophils, which are typical constituents of BP lesions. Cytokines and chemokines are responsible for the recruitment of immune cells to the site of inflammation; these include eosinophils, attracted by IL-5 and eotaxin-1, releasing toxic granules and proteases that cause tissue damage, and neutrophils, releasing ROS and proteolytic enzymes, worsening the blistering process. BP autoantibodies, composed of IgG1 and IgG4 subclasses, activate the complement system and consequently may produce anaphylatoxins that attract inflammatory cells to the dermo-epidermal junction and cause direct tissue injury at the basement membrane level. Proteases released from the recruited immune cells may further degrade components of the dermo-epidermal interface, leading to blister development.

Accurate diagnosis of Bullous Pemphigoid (BP) and Fixed Drug Eruption (FDE) is required. Understanding the clinical features of both would be essential for accurate distinction, as they share some overlapping symptoms but differ significantly in their pathophysiology, triggers, and treatment (Nino *et al.*, 2009). Despite the distinct differences between BP and FDE, there are several overlapping features that can create diagnostic challenges:

Both BP and FDE can present with blistering lesions, making it difficult to immediately distinguish between the two based solely on clinical appearance. Both conditions can begin with erythematous or urticarial plaques before progressing to blister formation (Cozzani *et al.*, 2015). So, a thorough clinical history is essential for bullous pemphigoid. The history of medication use and, in the case of FDE, a clear association with drug intake and reoccurrence of lesions at the same site would be more variable.

3. Pathophysiology of Bullous Pemphigoid

An autoimmune disorder linked to IgG autoantibodies against the BMZ, referred to as BP. Major antigens targeted in BP are BP180, a transmembrane protein, and BP230, an intracellular part of the hemidesmosome plaque (Marzano *et al.*, 2011). The epitopes recognized by the majority of the pathogenic IgG autoantibodies occur in the NC16a domain of BP180, which represents the extracellular region nearest to the basal cell membrane. About 85% of patients have serum autoantibodies that react with the NC16a domain of BP180 during the active disease phase.

The suggested mechanism of blister formation includes autoantibody binding to BP180, which results in local inflammatory cell infiltration due to complement activation and the release of proteolytic enzymes. Another mechanism is that the autoantibody binding results in the internalization of the antigen into basal cells, leading to fragility at the BMZ (Hammers & Stanley, 2016).

In contrast, BP230 mainly interacts with the C-terminal region, but the role of anti-BP230 antibodies in blister formation is not clear. IgE autoantibodies against the BMZ can also be detected by direct or indirect immunofluorescence tests. The degree of erythema or wheals in BP has been linked to serum IgE autoantibody levels, indicating a potential function for these antibodies in disease pathophysiology.

Pathologically and through laboratory investigations, the clinically edematous erythema with tense bullae is confirmed for BP (Stavropoulos *et al.*, 2014).

4. Diagnostic Approaches in Differentiating Bullous Pemphigoid and Fixed Drug Eruption

Due to their similar clinical appearances, the diagnosis of BP and FDE can be challenging (refer to Figure 2). Accurate distinction is possible, nonetheless, because of notable variations in their histological results (refer to Table 1), immunological profiles (refer to Table 2), and clinical settings (refer to Table 3).

Table 1: Histopathological differentiation between Fixed Drug Eruption (FDE) and Bullous Pemphigoid (BP)

Fixed drug eruption	Bullous pemphigoid
Basal Cell Necrosis FDE lesions show localized cytotoxicity in response to a particular treatment, as evidenced by the necrosis of basal keratinocytes in the epidermis. In extreme instances, the necrosis causes superficial blistering and epidermal separation.	**Subepidermal Blisters** Formation of blisters beneath the epidermis due to partition at the dermal-epidermal junction is characteristic of BP. The most direct cause of this separation is auto antibody-mediated breakdown of essential hemidesmosome components BP180 and BP230

Lymphocytic Infiltrates FDE is characterized by perivascular lymphocyte infiltration in the dermis, which suggests a delayed hypersensitivity reaction. In contrast to BP, eosinophils are usually not seen.	**Eosinophilic Infiltrate** BP is distinguished by a dense inflammatory infiltration of eosinophils in the dermis. Neutrophils may also occasionally be found, particularly in early lesions.
Pigmentary Alterations Post-inflammatory hyperpigmentation is frequent, and throughout the healing period, melanin-rich macrophages can be seen in the dermis.	**Edema and Inflammation** The upper dermis often demonstrates edema and mixed inflammatory cell infiltrates, further supporting the diagnosis.

Table 2: Immunological Differentiation between Fixed Drug Eruption (FDE) and Bullous Pemphigoid (BP)

Fixed Drug Eruption	Direct Immunofluorescence (DIF) in BP
Absence of Autoantibodies FDE does not involve an autoimmune mechanism, so tests like DIF and IIF are typically negative. The diagnosis of FDE relies on clinical history and histopathology rather than immunological evidence.	**Gold standard** test for BP diagnosis. It detects immune deposits at the dermal-epidermal junction. Linear deposits of IgG and/or C3 are seen along the basement membrane zone. This pattern differentiates Bullous Pemphigoid from other autoimmune blistering diseases and hypersensitivity reactions
	Indirect Immunofluorescence (IIF) in BP IIF detects circulating autoantibodies (anti-BP180 and anti-BP230) in the patient's serum. Salt-Split Skin Technique: This specialized IIF method localizes the autoantibodies to the roof of the salt-split blister, confirming BP. NOTE: Useful in cases where DIF findings are equivocal.

Table 3: Summary of Differentiating Factors between FDE and BP.

Parameters	FDE	BP
Pathogenesis	Drug-induced delayed hypersensitivity	Autoimmune targeting of BP180 and BP230
Histopathology	Basal cell necrosis, lymphocytic infiltrates	Subepidermal blisters, eosinophilic infiltrates
Immunological Testing	Negative immunofluorescence	Positive DIF and IIF findings
Lesion Distribution	Localized, recurring at the same site	Generalized, often widespread
Triggers	Always associated with a specific drug	May be spontaneous or drug-induced
Healing and Residuals	Heals with post-inflammatory hyperpigmentation	May scar or heal without pigment changes

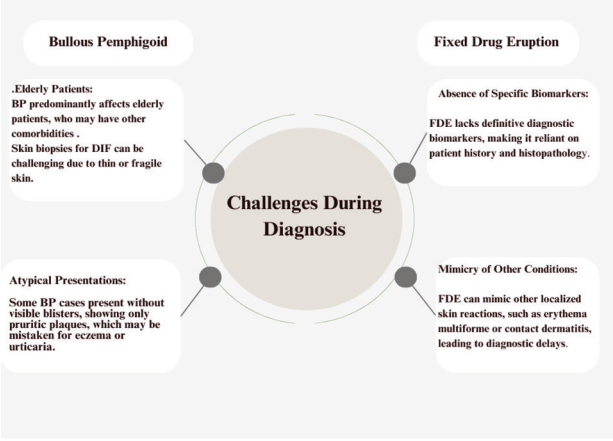

Figure 2: Demonstrating the Challenges being faced during the Diagnosis of Bullous Pemphigoid and Fixed Drug Eruption

5. Management of Bullous Pemphigoid and Fixed Drug Eruption

Due to their different underlying processes and clinical manifestations, bullous pemphigoid (BP) and fixed drug eruption (FDE) necessitate different methods for therapy. FDE is mostly treated by avoiding the causing medication and focusing on symptom alleviation, but BP involves autoimmune processes that call for immunosuppressive medications and anti-inflammatory medications, the primary goal being to control the autoimmune-driven inflammation, alleviate the symptoms, and prevent disease-related complications (Lo Schiavo *et al.*, 2013). Immunosuppressive and anti-inflammatory therapies alone or in combination can be useful depending upon the condition of the disease and the patient's health to control bullous pemphigoid.

5.1. Non-Pharmacological Treatment

Lifestyle changes and supportive care are essential elements of bullous pemphigoid management. These interventions prioritize skin care, nutritional assistance, infection prevention, and psychological well-being to not only improve patient outcomes but also raise people's quality

of life in general. Comprehensive care that is suited to each patient's particular requirements is ensured by a multidisciplinary approach comprising dermatologists, nutritionists, and mental health specialists (refer to Figure 3) (Agarwala *et al.*, 2016).

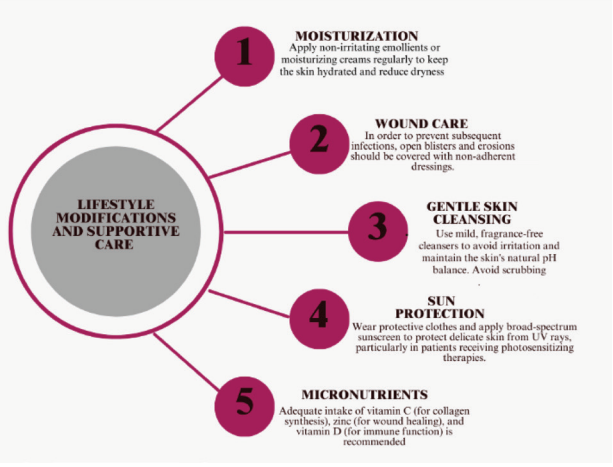

Figure 3: Lifestyle Modification to be considered for Improving Quality Of Life during Bullous Pemphigoid and Fixed Drug Eruption.

5.2. Pharmacological Treatment

Recognizing BP as an autoimmune disorder rather than an FDE ensures appropriate therapeutic strategies are implemented (refer Table 4), improving patient outcomes and avoiding unnecessary treatments.

Table 4: Pharmacological Therapy of Bullous Pemphigoid and Fixed Drug Eruption

Medications	Dose	Indication
Corticosteroids (First line therapy)		
Topical Corticosteroids		
Clobetasol Propionate 0.05%	10-30grams per day	Treat localized or mild to moderate bullous pemphigoid
Systemic Corticosteroids		
Prednisone	0.51 to 1.1 milligram per kilogram per day NOTE: (may vary depending upon severity and extent)	Function: suppress inflammatory response and reduce blister formation and helps in controlling inflammation
Biological Therapies		
Rituximab	Weekly: 375 mg/m² for 4 weeks	A monoclonal antibody targeting CD20+ B-cells, acts by reducing autoantibody production
Dupilumab	Administered subcutaneously, 300 milligram every 2 weeks	An interleukin-4 and interleukin -13 receptor antagonist approved for atopic dermatitis, in BP it shows its action by reducing pruritus and inflammation.
Immunosuppressive Agents		
Azathioprine	1-3 mg/kg/day	Used as the adjunct with corticosteroids in moderate-to-severe cases of BP.
Mycophenolate Mofetil (MMF)	1-2 g/day, with a favourable safety profile	Antimetabolite with immunosuppressive properties, MMF is a preferred choice in patients intolerant to azathioprine.
Methotrexate	10-25 mg weekly	A folic acid antagonist that suppresses lymphocyte proliferation, used at a lower dose in patient with BP
Cyclophosphamide	1.1-1.5 mg/kg/day	A cytotoxic agent reserved for severe refractory BP (Limited use)
Antibiotics		
Doxycycline	100 mg twice daily.	Reduce inflammation and blister formation with a better safety profile.
Adjunctive Therapies		
Antihistamines (Cetirizine, loratadine, or diphenhydramine.)	300 mg per day	Used to alleviate pruritus and improve patient comfort.
Topical Emollients	As per requirement	Prevent secondary infections, and promote wound healing.

6. Drug-Induced Bullous Pemphigoid (DIBP)

DIBP, a specific type of bullous pemphigoid, is a blistering condition (autoimmune) marked by subepidermal blisters and the deposition of autoantibodies in the BMZ (Sharma *et al.*, 2022).

DIBP develops when certain drugs (refer to figure 3) act as triggers for the start of the illness in genetically susceptible individuals, whereas BP is often known as an autoimmune syndrome. This occurrence demonstrates the complex relation within the host's immune system and external stimuli; medicines, diuretics, antibiotics, and DPP-4 inhibitors are amongst the growing list of drugs that have been linked in recent years to causing or worsening BP (Patel *et al.*, 2020).

By changing BMZ proteins like BP180 and BP230, these medications can trigger immunological reactions that resemble the autoimmune activity observed in spontaneous Bullous Pemphigoid (Kanahara & Agrawal, 2016). DIBP poses unique diagnostic and therapeutic challenges due to its overlap with hypersensitivity reactions, including Fixed Drug Eruption (FDE). Both conditions can share drug associations and similar lesion morphology, complicating clinical identification. Understanding the underlying mechanisms of DIBP, particularly the genetic predispositions and immune pathways involved, is crucial for distinguishing it from other drug-induced skin conditions and for optimizing patient management (Bernard & Antonicelli, 2017).

Drug-induced bullous pemphigoid (DIBP) closely resembles idiopathic BP in many aspects but often exhibits unique clinical features that can aid in its differentiation. The hallmark of DIBP, similar to idiopathic BP, is the presence of tense, fluid-filled, subepidermal blisters (Vornicescu *et al.*, 2018).

These blisters are often distributed symmetrically across the trunk, extremities, and flexural areas, accompanied with red, inflamed plaques (Erythematous Plaques) surrounding the blisters, resembling urticarial lesions. These plaques are often more prominent in DIBP than in idiopathic BP, particularly when triggered by DPP-4 inhibitors (Della Torre *et al.*, 2012).

Certain drugs have been shown to cause or worsen bullous pemphigoid (BP) in genetically susceptible individuals, resulting in a condition known as drug-induced bullous pemphigoid. These medications affect immunological pathways, damage the structural integrity of the BMZ, or alter the immunogenicity of major BP antigens such as BP180 and BP230 (Miyamoto *et al.*, 2019).

Recognizing medications associated with DIBP is critical for timely diagnosis and management. In many cases, discontinuing the offending drug leads to symptom improvement, although immunosuppressive therapy may still be required (Saniklidou *et al.*, 2018). DIBP typically occurs in older adults, often after the age of 60 (Yan *et al.*, 2023). Males and females are equally impacted, while some research indicates that women are somewhat more likely to be afflicted. Age-related changes in the immune system, such as reduced immune tolerance and a slower immune response, may predispose older individuals to drug-induced autoimmune diseases.

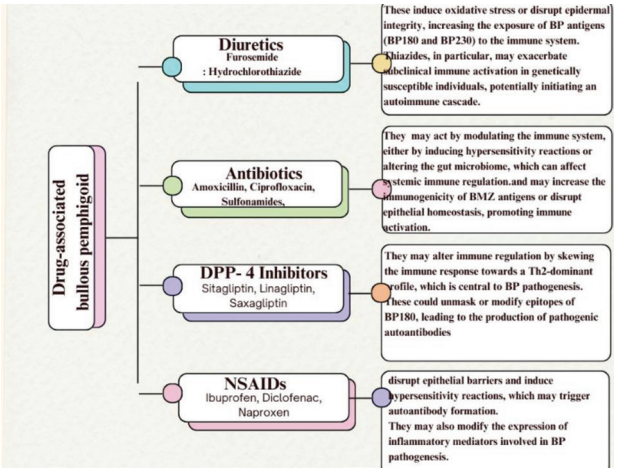

Figure 4: Schematic Representation of Drugs inducing DIBP (Drug Induced Bullous Pemphigoid)

6.1. Genetic Implications in DABP

DABP presents a subset of BP where specific medications serve as the leading factors in individuals underlying genetic predisposition. Also, advancements in pathogenesis and experimental methods have evolved with the significant understanding of the genetic vulnerability to BP (Agarwala *et al.*, 2016).

Several researchers have shown that BP is associated with certain Major Histocompatibility Complex (MHC) class II alleles. In addition to the HLADRβ1*04, HLA-DRβ1*1101, and HLA-BDB1*0302 alleles, the populations have a strong link with the human leukocyte antigen-DQβ1*0301 allele.

It was hypothesized that HLA alleles contribute to BP susceptibility in order to help T lymphocytes display basement membrane zone (BMZ) antigens. These HLA alleles are linked to the identification of conserved BMZ antigen epitopes in BP patients, which aids in the development of autoimmunity. (Marzano *et al.*, 2011).

7. Etiology for DIBP

In those who are genetically susceptible, drugs are considered to function as triggers, altering the antigenic properties of

the epidermal BMZ or boosting the immune response. By binding to molecules in the lamina lucida of the BMZ, drugs can alter these antigenic properties, acting as neoantigens and promoting the development of antibomb antibodies. On the other hand, they may alter molecules structurally and reveal previously hidden epitopes, which would trigger an immune reaction. (Stavropoulos *et al*., 2014).

Evidence from BP and other related bullous dermatoses supports the "two-step" approach, which postulates that two distinct medications may cause the condition (Patel *et al*., 2020). Table 4 discusses the clinical course of DABP.

7.1. Phenol-Based Medications

Aspirin and cephalosporins are among the phenol drugs linked to DIBP. These medications have been connected to blistering autoimmune diseases. The BMZ is disrupted via a process akin to that of drug-associated bullous pemphigoid, which exposes hidden epitopes that permit the manufacture of autoantibodies. Likewise, a causal association with aspirin has been proposed, whereby aspirin may function as a hapten, altering the lamina lucida's antigenicity or binding to cellular target sites, leading to the formation of autoantibodies (Kanahara & Agrawal, 2016).

7.2. Thiol-Based Medications

Sulfhydryl groups are present in or released by the precursors or catabolized metabolites of most thiol medications. Antibodies can develop as a result of thiol medications' ability to change molecules to act as haptens or disclose epitopes. By reacting with sulfhydryl groups in desmosomes, thiol medications can break the dermo-epidermal link in the BMZ (Vornicescu *et al*., 2018). Penicillamine and other thiol drugs can impair regulatory T cell activity, which increases the production of autoantibodies against BMZ antigens. Together, these mechanisms hasten the onset of illness. (Miyamoto *et al*., 2019).

Table 4: Representation of Progression stages of Drug Associated Bullous -Pemphigoid

Clinical Progression	Resolution
Acute Onset	DIBP usually manifests as an increasing eruption of tight blisters on the skin, followed by erythema and urticaria. These lesions often arise on the flexural surfaces, belly, and thighs, but they can occur elsewhere on the body.
Spontaneous Resolution with Drug Withdrawal	The characteristic of DIBP is that it frequently resolves after discontinuing the offending substance. Improvement might take weeks or months, depending on the severity of the disease and the individual's immunological response. However, in extreme situations, systemic corticosteroids or immunosuppressive drugs may be necessary.
Relapses	If the triggering drug is reintroduced, relapse is common, and the lesions will recur at the same site. Therefore, a clear identification of the causative drug is essential to avoid further drug exposure.
Chronicity	Unlike idiopathic BP, which can be lifelong, DIBP often has a better prognosis, with full remission once the medicine is discontinued. Chronic instances may still exist, especially if several medicines contribute to illness development.

Currently, over 90 drugs are associated to the elevated BP. However, base reason of medication reaction is yet unidentical, Studies are being going on to understand the mechanisms behind them (Yan *et al*., 2023). Studying the medicines linked to BP can help physicians diagnose and treat DABP early on. To address ethical and safety considerations, it is not practicable to ask patients to confirm the preliminary link between their Bullous Pemphigoid and the offending medicine.

8. DIBP Management

Table 5: Representing Pharmacological and Non-Pharmacological interventions for DABP

Management	Indications
Pharmacological Interventions	
Topical Corticosteroids	For localized or mild cases, useful as adjunct therapy in systemic treatment, e.g.: Clobetasol propionate
Systemic Corticosteroids	Low to moderate doses e.g., prednisone 0.51–1.1 mg/kg/day.
Biologics	Targets autoantibody-producing B cells e.g.: rituximab in refractory or severe cases.

Immunosuppressive Agents	Severe or refractory cases that are unresponsive to corticosteroids.
Drug Discontinuation	Immediate withdrawal of the suspected offending drug. Common drugs include: diuretics, NSAIDs, antibiotics, DPP-4 inhibitors
Non-Pharmacological Interventions	
Dietary Modifications	Calcium and vitamin D supplementation along with balanced diet
Skin Care	Use emollients and moisturizers to maintain skin hydration

The field of drug-induced bullous pemphigoid (DIBP) has evolved significantly, but many aspects of its pathophysiology, diagnosis, and management remain poorly understood. Accurate and early diagnosis of DIBP is essential for effective management. Emerging diagnostic tools and biomarkers offer promise in improving diagnostic accuracy: (Yan *et al*., 2023).

- The Presence of Biomarkers for Early Detection: Detection of BP180 and BP230 autoantibodies using ELISA or immunoblotting might be used to differentiate DIBP from idiopathic BP.
- Cytokine levels: Elevated levels of some cytokines (e.g., IL-17, IL-23) may act as indicators for inflammation in DIBP.
- Imaging techniques: Reflectance confocal microscopy (RCM) is an advanced imaging technique that can give real-time, non-invasive viewing of blister structures and immune cell infiltration.
- Modern Molecular Diagnostics: Direct and indirect immunofluorescence remain the gold standard for BP diagnosis; however, using molecular methods such as polymerase chain reaction (PCR) to determine genetic predispositions may improve diagnostic accuracy (Agarwala *et al*., 2016).

8. Research Insights and Future Directions

The understanding of FDE and BP has emerged to a greater extent, whereas considerable gaps still exist in DABP. In further research to understand BP and DIBP, the focus must be on unravelling the molecular and genetic pathways involved, including the complex interplay of medicines, immunological responses, and genetic variables. BP must be differentiated from DIBP and FDE, in which identification of such biomarkers would assist to reach proper diagnosis accurately and without delays. Diagnostic approaches should further evolve for improved clinical accuracy—improvements in methods that use immunofluorescence and histological examinations. Additionally, personalization based on genetic profiling of an individual through adjustments of immunosuppressive medications with consideration to respective pharmacological responses indicates prospects for a better, targeted form of therapy. The research avenues outlined above will play critical roles in determining how more patients' results improve through future therapy with better effects in treating BP and DIBP.

Abbreviations

FDE: Fixed Drug Eruption; **DIBP:** Drug Induced Bullous Pemphigoid; DABP: Drug Associated Bullous Pemphigoid; DPP-4: Dipeptidyl Peptidase-4 Inhibitors; **PCR:** Polymerase Chain Reaction; **BP230:** Bullous Pemphigoid 230 Antibody; **DIF:** Direct Immunofluorescence; **BP180:** Bullous Pemphigoid 180; **IDIF:** Indirect Immunofluorescence; **BMZ:** Basement Membrane Zone; **IL-15:** Interleukin-15; **CD8+T-Cells:** Cytotoxic T Cells; **RCM:** Reflectance Confocal Microscopy.

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Authorship Contribution

Designing of manuscript: Adarsh Kesari, Kriti Jain, Roshan Pandey, Ayush Mishra; Analysis of the data: Amit Sharma, Sarita Jangra; Editing of the manuscript: Bisman, Bhavesh Dharmani; Critically review of the article: Thakur Gurjeet Singh; Amit Sharma and Sarita Jangra; Supervision: Thakur Gurjeet Singh.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

References

Agarwala, M., Mukhopadhyay, S., Sekhar, Mr., & Dincy Peter, C. (2016). Bullous fixed drug eruption probably induced by paracetamol. *Indian Journal of Dermatology*, *61*(1), 121. https://doi.org/10.4103/0019-5154.174098

Alpsoy, E., Akman-Karakas, A., & Uzun, S. (2015). Geographic variations in epidemiology of two autoimmune bullous diseases: pemphigus and bullous pemphigoid. *Archives of Dermatological Research*, *307*(4), 291–298. https://doi.org/10.1007/s00403-014-1531-1

Baican, A., Baican, C., Chiriac, G., Chiriac, M. T., Macovei, V., Zillikens, D., Ciuce, D., & Sitaru, C. (2010). Pemphigus vulgaris is the most common autoimmune bullous disease in Northwestern Romania. *International Journal of Dermatology*, *49*(7), 768–774. https://doi.org/10.1111/j.1365-4632.2009.04345.x

Bernard, P., & Antonicelli, F. (2017). Bullous Pemphigoid: A Review of its Diagnosis, Associations and Treatment. *American Journal of Clinical Dermatology*, *18*(4), 513–528. https://doi.org/10.1007/s40257-017-0264-2

Cozzani, E., Gasparini, G., Burlando, M., Drago, F., & Parodi, A. (2015). Atypical presentations of bullous pemphigoid: Clinical and immunopathological aspects. *Autoimmunity Reviews*, *14*(5), 438–445. https://doi.org/10.1016/j.autrev.2015.01.006

Della Torre, R., Combescure, C., Cortés, B., Marazza, G., Beltraminelli, H., Naldi, L., & Borradori, L. (2012). Clinical presentation and diagnostic delay in bullous pemphigoid: a prospective nationwide cohort. *British Journal of Dermatology*, *167*(5), 1111–1117. https://doi.org/10.1111/j.1365-2133.2012.11108.x

Hammers, C. M., & Stanley, J. R. (2016). Mechanisms of Disease: Pemphigus and Bullous Pemphigoid. *Annual Review of Pathology: Mechanisms of Disease*, *11*(1), 175–197. https://doi.org/10.1146/annurev-pathol-012615-044313

Holgate, S., Smith, N., Massanari, M., & Jimenez, P. (2009). Effects of omalizumab on markers of inflammation in patients with allergic asthma. *Allergy*, *64*(12), 1728–1736. https://doi.org/10.1111/j.1398-9995.2009.02201.x

Kanahara, S. M., & Agrawal, A. (2016). Drug-induced bullous pemphigoid. *Journal of General Internal Medicine*, *31*(11), 1393–1394. https://doi.org/10.1007/s11606-016-3679-1

Kershenovich, R., Hodak, E., & Mimouni, D. (2014). Diagnosis and classification of pemphigus and bullous pemphigoid. *Autoimmunity Reviews*, *13*(4–5), 477–481. https://doi.org/10.1016/j.autrev.2014.01.011

Langan, S. M., Smeeth, L., Hubbard, R., Fleming, K. M., Smith, C. J. P., & West, J. (2008). Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study. *BMJ*, *337*(jul09 1), a180–a180. https://doi.org/10.1136/bmj.a180

Lo Schiavo, A., Ruocco, E., Brancaccio, G., Caccavale, S., Ruocco, V., & Wolf, R. (2013). Bullous pemphigoid: Etiology, pathogenesis, and inducing factors: Facts and controversies. *Clinics in Dermatology*, *31*(4), 391–399. https://doi.org/10.1016/j.clindermatol.2013.01.006

Marzano, A. V, Tedeschi, A., Berti, E., Fanoni, D., Crosti, C., & Cugno, M. (2011). Activation of coagulation in bullous pemphigoid and other eosinophil-related inflammatory skin diseases. *Clinical and Experimental Immunology*, *165*(1), 44–50. https://doi.org/10.1111/j.1365-2249.2011.04391.x

Miyamoto, D., Santi, C. G., Aoki, V., & Maruta, C. W. (2019). Bullous pemphigoid. *Anais Brasileiros de Dermatologia*, *94*(2), 133–146. https://doi.org/10.1590/abd1806-4841.20199007

Nanda, A., Dvorak, R., Al-Saeed, K., Al-Sabah, H., & Alsaleh, Q. A. (2004). Spectrum of autoimmune bullous diseases in Kuwait. *International Journal of Dermatology*, *43*(12), 876–881. https://doi.org/10.1111/j.1365-4632.2004.02292.x

Nino, M., Francia, M. G., Costa, C., & Scalvenzi, M. (2009). Bullous Fixed Drug Eruption Induced by Paracetamol: Report of a Pediatric Case. *Case Reports in Dermatology*, *1*(1), 56–59. https://doi.org/10.1159/000243728

Patel, S., John, A. M., Handler, M. Z., & Schwartz, R. A. (2020). Fixed Drug Eruptions: An Update, Emphasizing the Potentially Lethal Generalized Bullous Fixed Drug Eruption. *American Journal of Clinical Dermatology*, *21*(3), 393–399. https://doi.org/10.1007/s40257-020-00505-3

Saniklidou, A. H., Tighe, P. J., Fairclough, L. C., & Todd, I. (2018). IgE autoantibodies and their association with the disease activity and phenotype in bullous pemphigoid: a systematic review. *Archives of Dermatological Research*, *310*(1), 11–28. https://doi.org/10.1007/s00403-017-1789-1

Schmidt, E., & Zillikens, D. (2013). Pemphigoid diseases. *The Lancet*, *381*(9863), 320–332. https://doi.org/10.1016/S0140-6736(12)61140-4

Sharma, A., Baldi, A., & Sharma, D. K. (2022). Levofloxacin induced bullous fixed drug eruption: a rare case report. *European Journal of Hospital Pharmacy*, *29*(e1), e95–e96. https://doi.org/10.1136/ejhpharm-2020-002566

Stavropoulos, P. G., Soura, E., & Antoniou, C. (2014). Drug-induced pemphigoid: a review of the literature. *Journal of the European Academy of Dermatology and Venereology*, *28*(9), 1133–1140. https://doi.org/10.1111/jdv.12366

Taquin, H., Chiaverini, C., & Lacour, J. P. (2016). Spectrum of Clinical Responses to Therapies in Infantile Bullous Pemphigoid. *Pediatric Dermatology*, *33*(2). https://doi.org/10.1111/pde.12779

Ujiie, H., Nishie, W., & Shimizu, H. (2011). Pathogenesis of Bullous Pemphigoid. *Dermatologic Clinics*, *29*(3), 439–446. https://doi.org/10.1016/j.det.2011.03.008

Verheyden, M., Bilgic, A., & Murrell, D. (2020). A Systematic Review of Drug-Induced Pemphigoid. *Acta Dermato Venereologica*, *100*(15), adv00224. https://doi.org/10.2340/00015555-3457

Vornicescu, C., Şenilă, S., Cosgarea, R., Candrea, E., Pop, A., & Ungureanu, L. (2018). Pemphigoid nodularis - rare presentation of bullous pemphigoid: A case report and literature review. *Experimental and Therapeutic Medicine*. https://doi.org/10.3892/etm.2018.7057

Yan, T., Xie, Y., Liu, Y., Shan, Y., Wu, X., Wang, J., Zuo, Y.G., & Zhang, Z. (2023). Dupilumab effectively and rapidly treats bullous pemphigoid by inhibiting the activities of multiple cell types. *Frontiers in Immunology*, *14*, 1194088. https://doi.org/10.3389/fimmu.2023.1194088

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