Insights into bullous pemphigoid: A comprehensive review of diagnostic modalities

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Bullous pemphigoid (BP) is an autoimmune blistering disorder associated with profound morbidity. Timely diagnosis of BP is critical for early initiation of therapies, but diagnosis of BP is often challenging. As the pathophysiology of BP has been further elucidated, new diagnostic modalities have been developed. However, it remains unclear which modalities are the most effective for diagnosing BP. In this review article, we provide an updated overview of BP diagnostic modalities, comparing their reported sensitivities and specificities as well as proposing a diagnostic algorithm to help dermatologists navigate diagnosing this complex disease. (JAAD Reviews 2025;3:26-36.)

Key words: bullous pemphigoid; complement; diagnostics; direct immunofluorescence; dermatoscopy; ELISA; eosinophils; immunofluorescence; immunoglobulin; immunohistochemistry; indirect immunofluorescence.

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering disorder that commonly affects older individuals. Classically, patients present with tense, pruritic bullae although nonbullous clinical variants have been described.[1,2] Timely diagnosis of BP is critical as it is a chronic, relapsing disease associated with significant morbidity.[3] In this review, we summarize standard and emerging diagnostic modalities and propose a diagnostic algorithm for BP.

Hematoxylin and eosin staining

Hematoxylin and eosin (H&E) staining is a routine diagnostic procedure for BP. The ideal biopsy type depends on lesion size and morphology.[4] For small vesicles, punch biopsy capturing the entire vesicle is preferred. For large bullae, punch biopsy involving the blister edge and/or intact, inflamed skin is recommended.[4] If no bullae are present, punch biopsies of inflammatory lesions can be obtained. Classic histopathological features include subepidermal blistering, with numerous eosinophils located within the blister cavity or lining the dermoepidermal junction.[5-9] Eosinophilic spongiosis and early subepidermal blisters may be seen in early lesions or in urticarial or eczematous BP lesions.[9] Other less frequent findings include dermal edema with perivascular eosinophils, re-epithelization, and blister roof necrosis.[2,4,9-11] Histology of nonbullous variants is generally nonspecific. Thus, the use of H&E alone for BP diagnosis is not recommended.

Direct immunofluorescence

Direct immunofluorescence (DIF) is the gold standard diagnostic modality given its high sensitivity and specificity (Table I).[12-14] Through application of antibody-conjugated fluorophores to biopsied tissue, DIF can detect antibodies and complement fixed to tissue. Linear deposits of

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complement 3 (C3) and/or IgG along the basement membrane are characteristic of BP, but can also be seen in epidermolysis bullosa acquisita (EBA) and mucous membrane pemphigoid (MMP).[15-21] Tissue is sent in specialized transport media such as Michel's or Zeus' media (or saline if delivered within 24 hours) for immunofluorescence testing; formalin-fixed tissue is not acceptable.

The ideal location for biopsy remains unclear, although perilesional biopsy is the classic location as an intact basement membrane zone is necessary for accurate interpretation. Blistered skin or skin with secondary changes should be avoided for biopsy as inflammation may consume *in vivo* bound antibodies leading to false negative staining.[15,22] Biopsies from lesional, nonbullous skin may have an increased likelihood of positive DIF than other sites.[4,17,18,23] Recommendations to avoid lower extremity biopsies due to increased risk of false-negative results have been challenged, with one study finding no difference in false-negative results among these biopsy sites.[24-26]

CAPSULE SUMMARY

- This review explores several modalities with variable utility for diagnosing bullous pemphigoid, including direct and indirect immunofluorescence, enzyme-linked immunosorbent assay, complement immunohistochemistry, eosinophil counts, and dermatoscopy.
- Evaluating each diagnostic modality and proposing a diagnostic algorithm may assist dermatologists in effectively incorporating newer, underutilized methods into their clinical practice.

Atypical staining patterns and interreader variability may also obfuscate DIF interpretation. Although DIF remains the gold standard, sole reliance may lead to misdiagnosis.[27] In patients with negative DIF, testing with other diagnostic modalities or potentially repeating the biopsy is recommended, particularly if BP is strongly suspected.

Indirect immunofluorescence

Indirect immunofluorescence (IIF) uses patients' serum to detect circulating autoantibodies.[28] Tissue substrates are incubated with serum followed by incubation with secondary fluorophore-conjugated antibodies.[17] IIF is considered less reliable than DIF because of its lower sensitivity (Table I).[29] IIF does not discriminate between specific self-antigens and the value of obtaining serial IIF titers to monitor BP disease activity is debated.[30] However, for patients who decline skin biopsy, IIF is a viable alternative.[31,32]

IIF uses a variety of substrates for diagnostic testing with varying sensitivities.[33] Salt split skin (SSS-IIF), named for its split lamina lucida, is a commonly used substrate that allows for the differentiation of BP from other clinically similar blistering disorders such as EBA, anti-p200 pemphigoid, and anti-p105 pemphigoid. SSS-IIF of BP characteristically shows an epidermal/roof staining pattern, whereas EBA, anti-epiligrin MMP, anti-p200, and anti-p105 demonstrate dermal/floor staining.[34-36] SSS-IIF substrate has the highest reported sensitivity for BP diagnosis, ranging from 74% to 97%.[37-40] Of note, SSS-DIF is also available and can be helpful for distinguishing rare forms of pemphigoid such as anti-p200 and anti-p105; however, this assay is not widely offered due to technical difficulty.[41] Lower sensitivity substrates include normal human skin, rat bladder epithelium, and monkey esophagus.[29,42,43]

The Biochip Mosaic IIF represents a novel diagnostic technique for BP. Through containing multiple incubation fields with tissue substrates and transfected cell lines with specific antigen targets for polyvalent testing, the Biochip Mosaic IIF provides diagnostic antibody profiles in a single incubation.[44] When compared with DIF, Biochip Mosaic IIF showed high sensitivity (94.4%-100%) and specificity (94.3%-100%).[45,46] Unfortunately, this is not currently commercially available in the United States.

Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA) is a serum test that measures autoantibodies against specific target antigens. ELISA is ideal for patients requiring noninvasive or secondary diagnostic testing due to negative DIF.[47,48] Unlike IIF, ELISA can discriminate BP-specific target antigens, BP180 IgG and BP230 IgG, and levels correlate with disease severity, making it a valuable tool for assessing disease activity and treatment response.[49-53] Commercially, ELISA testing for BP180 and BP230 IgG is typically offered together. ELISA for BP180 IgG shows high specificity and variable sensitivity for BP diagnosis, whereas BP230 IgG typically demonstrates high specificity but low sensitivity (Table I).[49,54]

The noncollagenous region 16 A (NC16A) domain is an immunodominant pathogenic epitope in classic BP. Testing for anti-BP180NC16A IgG is efficacious for BP diagnosis given its high specificity and sensitivity.[55-59] It is typically the standard antibody

Abbreviations used:

BP:	bullous pemphigoid
C3:	complement 3
C4:	complement 4
DIF:	direct immunofluorescence
EBA:	epidermolysis bullosa acquisita
ELISA:	enzyme-linked immunosorbent assay
H&E:	hematoxylin and eosin
Ig:	immunoglobulin
IHC:	immunohistochemistry
IIF:	indirect immunofluorescence
MMP:	mucous membrane pemphigoid
NC16A:	noncollagenous region 16 A
SSS-IIF:	salt split skin indirect immunofluorescence

assay for evaluation of BP180 across the United States.[60] The high discriminative value of this antigen is evidenced by its ability to diagnose BP using saliva.[61] Because BP180 autoantibodies are not restricted to NC16A, patients with BP have false-negative results with NC16A-specific testing, highlighting the utility of full BP180 ELISA testing to increase sensitivity.[62,63]

Although ELISA and IIF demonstrate utility for diagnosis, they may miss patients with atypical or non-BP because these patients may not have detectable circulating antibodies or may have rare antibody classes (such as immunoglobulin E [IgE]) that are not commonly tested on assays. Therefore, if a patient with atypical BP has a positive DIF but negative serology, this should not dissuade clinicians from making a BP diagnosis. On the other hand, false-positive results with ELISA have also been noted, with one study reporting a 7.4% prevalence of positive BP antigens among patients without BP.[64] Thus, ELISA alone is not sufficient to diagnose BP. ELISA may be underutilized due to gaps in clinical practice, poor access to laboratories that perform ELISA, and insurance restrictions.[65]

Blister fluid IIF and ELISA

BP autoantibodies have been detected in aspirated blister fluid. Consequently, IIF and ELISA of blister fluid have been suggested as alternative diagnostic methods. Sensitivities of blister fluid IIF range from 70% to 92%, without significant differences found between immunoreactivity of serum and blister fluid (Table I).[66-69] When both serum and blister fluid were used for IIF, diagnostic sensitivity increased.[68] Although most blister fluid and serum antibody levels correlate, there was one case where a patient with localized scalp blisters had positive blister fluid despite a negative serum IIF. This suggests that blister fluid IIF may be helpful for localized disease.[68]

Complement immunohistochemistry

The pathophysiology of BP is intricately linked to complement deposition. After complement degradation, C3d and C4d remain attached to target cells, serving as stable markers of complement activation.[70-73]

Immunohistochemistry (IHC) of C3d and C4d for BP diagnosis has potential advantages (Fig 1). These include obviating the need for a second biopsy for frozen sectioning since IHC uses formalin-fixed paraffin-embedded samples, not requiring DIF equipment, visualizing complement deposition directly on standard light microscopy of IHC, and cost-effectiveness.[71,72,74] Despite these advantages, complement IHC has yielded mixed results and is not universally available.

C3d IHC

In studies comparing C3d IHC with DIF for BP diagnosis, sensitivity of C3d IHC ranged widely (37%-97%) with high specificity (95.6%-100%) (Table I).[70-72,74-76] The presence of subepidermal and immunoreactive blisters on histology increased sensitivity.[72,76] Notably, some studies reported cases of positive C3d IHC when C3 DIF was negative.[72,75]

The variability in sensitivity of C3d IHC may be attributable to differing specimen handling methods, autoantibody clones, immunostaining protocols, and heterogeneity in interpretation of positive samples.[70-72,74-76]

C4d IHC

When BP is highly suspected despite negative DIF to both IgG and C3, use of C4d DIF or IHC may be helpful.[77] Studies exploring C4d IHC reported lower sensitivities than C3d IHC, ranging from 23.5% to 90% (Table I).[70,72,75,78-80] Differences in frequency and intensity of C3d and C4d staining may contribute to variability in their diagnostic utility.[70]

Complement IHC in combination with other diagnostic modalities

The utility of C3d and C4d IHC in combination with other diagnostic techniques has been investigated (Table II). C3d IHC and BP180/BP230 IgG ELISA may offer a cost-effective alternative to DIF.[81] Although the combined use of DIF and ELISA had the highest sensitivity (94.1%) in a study of 194 BP cases, the combination of C3d IHC and ELISA had a higher sensitivity (92.2%) than DIF alone (80%). Smaller studies exploring combined staining for IgG and C3d on IHC yielded variable results.[74,75]

Table I. Comparison of the reported sensitivity and specificity of individual bullous pemphigoid diagnostic modalities

Diagnostic modality	Diagnostic comparison	Sensitivity	Specificity
Direct immunofluorescence	Clinical	80%-96%	100%
	IIF, ELISA	63.1%-90%	95.6%-100%
Enzyme-linked immunosorbent assay			
BP180 IgG (including BP180NC16A) (serum)	DIF, clinical	53%-97.6%	94%-100%
	IIF, clinical	79%-95%	90%-98%
BP180 IgG (blister fluid)	DIF, clinical	61.5%-95.8%	
BP230 IgG (serum)	IIF, clinical	16%-72%	90%-98%
	DIF, clinical	14.6%-77.1%	62%-100%
BP230 IgG (blister fluid)	DIF, clinical	20%-30.8%	
BP180 and BP230IgG (serum)	DIF, clinical	66%-76.5%	89%-91.8%
	IIF	95%	
BP180 IgE (serum)		18%-65%	
Indirect immunofluorescence			
IIF (serum)	ELISA	70.4%-97.6%	99.8%-100%
IIF (blister fluid)	DIF, clinical	70%-92%	
IIF (serum and blister fluid)	DIF, clinical	96%	
BIOCHIP IIF BP180 IgG (serum)	ELISA	76.9%-100%	60%-100%
	IIF	83.33%	
	Immunoblotting	60%-97%	
	DIF	36%-81%	
BIOCHIP IIF BP180 IgG (blister fluid)	DIF	76.9%	
BIOCHIP IIF BP230 IgG (serum)	ELISA	43%-60%	98%-100%
Complement IHC			
C3d	DIF	37%-97%	95.6%-100%
	ELISA	74.1%	95.8%
C4d	DIF	23.5%-90%	86%-100%

DIF, Direct immunofluorescence; *IIF*, indirect immunofluorescence; *ELISA*, enzyme-linked immunosorbent assay; *IHC*, immunohistochemistry. Columns where values were not reported by studies are indicated by blank spaces.

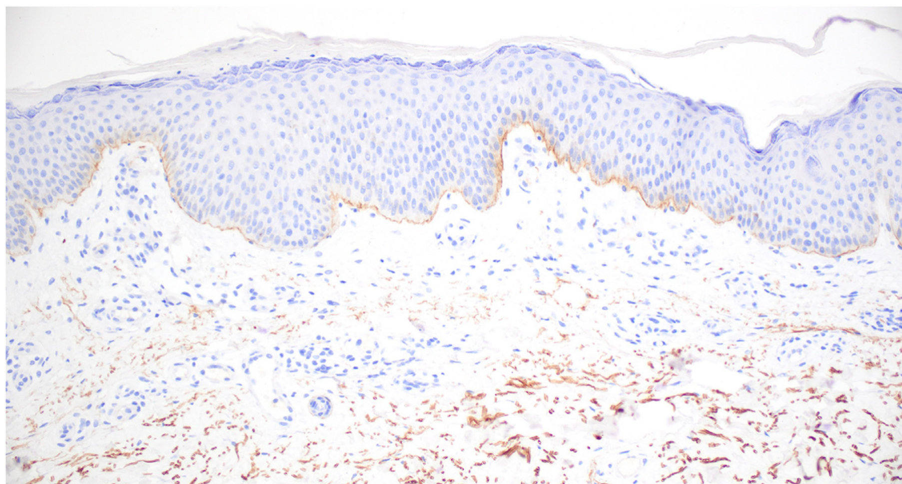

Fig. 1. C4d immunostain highlights linear deposition of complement along the dermo-epidermal junction in this case of urticarial bullous pemphigoid, mirroring what was seen with the perilesional C3 direct immunofluorescence study. (Cd immunostain; original magnification: ×200.)

Table II. Comparison of the sensitivity and specificity between combination of bullous pemphigoid diagnostic modalities

Combination of diagnostic modalities	Diagnostic comparison	Sensitivity	Specificity
SSS-IIF+ BP180 ELISA	Clinical	91.66%	
DIF + BP180 ELISA	Clinical	75.6%-94.1%	91.8%
SSS-IIF + DIF	Clinical	71.9%	
C3d IHC + BP180/BP230 ELISA	Clinical	92.2%	86.9%
IgG IHC + C3d IHC	DIF, clinical	76.7%-85%	75.6%-100%
IgG IHC + C4d IHC	DIF, clinical	81.1%	75.6%
IgG IHC + C4d IHC + C3d IHC	DIF, clinical	86.0%	
DIF + C3d IHC	Clinical	90.8%	86.8%

DIF, Direct immunofluorescence; *ELISA*, enzyme-linked immunosorbent assay; *IHC*, immunohistochemistry; *IIF*, indirect immunofluorescence; *SSS-IIF*, salt split skin indirect immunofluorescence.
Columns where values were not reported by studies are indicated by blank spaces.

Immunoglobulin E

IgE autoantibodies against hemidesmosomal antigens BP180 and BP230 may play a role in BP pathophysiology.[39,82-85] Anti-BP230 IgE has been linked to eosinophil accumulation,[85,86] whereas anti-BP180 IgE mediates mast cell and basophil degranulation resulting in inflammation and pruritus.[86-92]

Serologic measurement of BP180 IgE levels via ELISA has been reported (Table I).[93] BP180 IgE levels have correlated with BP progression, severity, extensive skin involvement, and remission time.[94-98]

Studies have suggested IgE's utility as an early marker of disease detectable prior to the development of characteristic skin lesions.[90,99-101] However, others have shown a minimal diagnostic impact of BP180 IgE when compared with BP180 IgG assay and ELISA IgE is not routinely available outside of research centers.[102]

Eosinophils

Eosinophils are the predominant inflammatory infiltrate in BP, with dermal eosinophilia sometimes preceding bulla formation.[8,103] Studies have found high levels of both eosinophilic chemokines and proteins in blister fluid and serum of patients with BP, with some reporting positive correlation between these levels and BP disease severity.[8,104-108]

About 50% to 60% of patients with BP have peripheral blood eosinophilia.[104,109] To our knowledge, no study has used eosinophil counts as a sole diagnostic measure for BP as it is nonspecific; however, some have evaluated the association of these measures with disease severity and phenotype. One study of 27 patients with BP found significant correlations between number of dermal eosinophils, serum levels of BP180/BP230 IgG measured by ELISA, and Bullous Pemphigoid Disease Activity Index scores.[110]

A study of 225 patients with BP found a significantly higher mean absolute peripheral blood eosinophil count among patients with BP than controls.[111] Positive associations between peripheral blood eosinophil count and BP distribution (palmoplantar > mucosal involvement) and disease severity were also noted.[111,112]

Dermatoscopy

Dermatoscopy is a potential noninvasive diagnostic tool for BP.[113-115] Dermatoscopic features of BP include yellow translucent backgrounds, hemorrhagic crusts, distorted pigment networks, diffuse scaling, and linear serpentine vessels.[113-115] Dermatoscopic features may overlap with other bullous diseases, so dermatoscopy alone is not sufficient for diagnosis.

DRUG-INDUCED VERSUS IDIOPATHIC BP

Although our review mainly focuses on idiopathic BP, a brief discussion on differentiating drug-induced from idiopathic disease is warranted given the similarities. Drug-induced BP has been reported secondary to several medications including gliptins and checkpoint inhibitors. Notably, checkpoint inhibitor induced BP may have a longer latency following initiation and may persist after medication discontinuation.[116-121]

Clinically, drug-induced BP may affect younger patients, have more mucosal involvement, resemble other diseases such as erythema multiforme. or have a positive Nikolsky sign.[122-125] Drug-induced BP should also be considered in patients with difficult-to-distinguish symptomology.[126] Histologically, idiopathic and drug-induced BP share several features; however, a greater degree of eosinophils, necrotic keratinocytes, and thrombi may be seen in iatrogenic disease.[125]

Drug-induced and idiopathic BP have similar immunofluorescence profiles and specific antigens differentiating drug-induced and idiopathic BP have

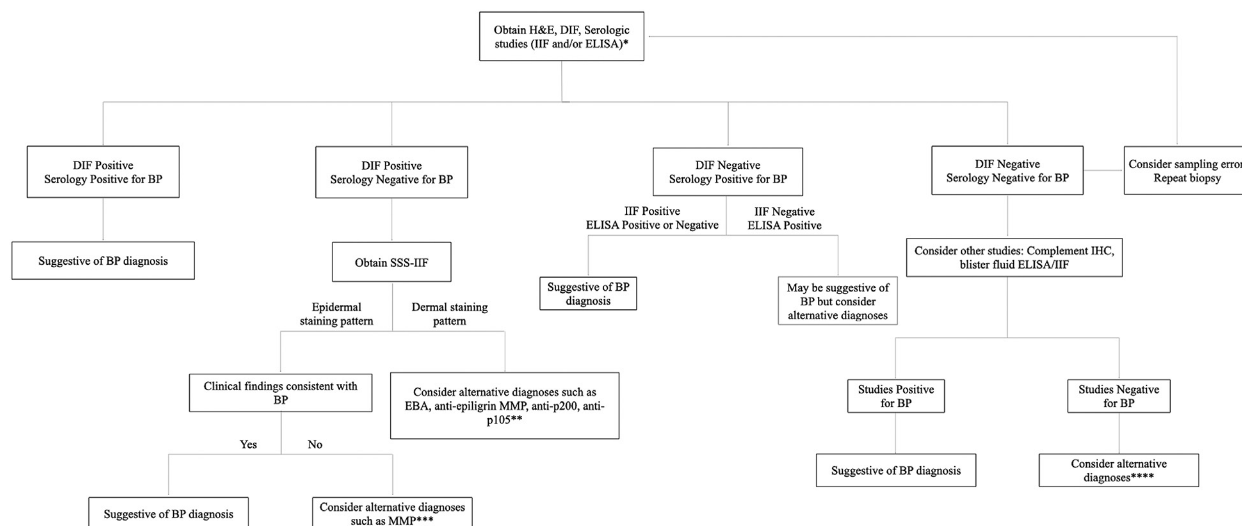

Fig. 2. Diagnostic algorithm for bullous pemphigoid. *BP*, Bullous pemphigoid; *DIF*, direct immunofluorescence; *EBA,* epidermolysis bullosa acquisita; *ELISA*, enzyme-linked immunosorbent assay; *H&E*, hematoxylin and eosin stain; *IHC*, immunohistochemistry; *IIF*, indirect immunofluorescence; *MMP*, mucous membrane pemphigoid; *SSS*, salt split skin. *In a patient with high clinical suspicion for BP, H&E, DIF, and serologic studies (IIF and/or ELISA) should be obtained. A thorough medical and drug history should also be done at this time. **EBA, anti-p200, and anti-p150 may present similarly as BP and may appear identical on DIF. If there is clinical suspicion for these diseases, SSS-IIF and/or ELISA can be used to distinguish them. Additional studies will be needed to distinguish these diseases from each other. ***MMP and BP can both have positive DIF and epidermal split pattern on SSS-IIF. Consideration of clinical features and MMP specific diagnostic tests are needed to differentiate these diseases. ****Alternative diagnoses may include other blistering diseases or pemphigoid variants.

not been identified.[126] Therefore, a thorough drug history should be obtained in all patients.

Differentiating BP from MMP

MMP is an autoimmune blistering disorder characterized by predominance of blisters on mucous membranes of the head/neck and anogenital regions.[127] Because patients with BP can also experience mucocutaneous involvement, MMP and BP are difficult to clinically distinguish.[128]

On histology, MMP and BP show subepidermal blistering, but the inflammatory infiltrate of MMP is typically more lymphoplasmacytic rather than eosinophil-rich as in BP. Additionally, later lesions of MMP often show scarring.[21] DIF of MMP demonstrates linear deposits of IgG, IgA, and/or C3 along the basement membrane zone, although the pathogenic antibodies of MMP fix complement less often, and thus both DIF and IHC are less likely to show complement subepithelial deposition.[21,72,127] IIF can be used to detect circulating MMP IgG autoantibodies, with staining seen on either the epidermal or dermal side in SSS-IIF depending on the detected autoantigen.[21,129,130] ELISA for detection of autoantibodies against MMP-predominant antigens, including laminin 332, collagen VII, collagen XVII (BP180), and BP230, is also available; however, due to the low titer and heterogeneity of MMP autoantibodies, false-negative results may occur.[21,130-132]

Given overlapping clinical and pathologic features, distinguishing MMP from BP with mucocutaneous involvement is challenging. Clinicians should consider BP and MMP in the differential diagnosis while evaluating mucosal-predominant disease and perform additional diagnostic testing for differentiation.

DISCUSSION AND CONCLUSION

The diverse array of diagnostic methodologies explored in our review article highlights the complexities of diagnosing BP. To help dermatologists navigate these complexities, we propose a potential diagnostic algorithm, depicted in Fig 2. In patients

with suspected BP, we recommend obtaining H&E, DIF, and serologic studies such as SSS-IIF and/or ELISA. As DIF findings are identical in BP, EBA, and other more rare pemphigoid entities, SSS-IIF and/or ELISA are necessary to distinguish these disorders. In SSS-IIF, an epidermal staining pattern is suggestive of BP. If a dermal staining pattern results, alternative diagnoses such as EBA, anti-p200, anti-epiligrin MMP, or anti-p105 should be considered and appropriate diagnostic studies such as ELISA performed. A negative DIF with positive serologies may be suggestive of BP, but serological false positives should be considered. If both DIF and serologies are negative, one can consider evaluation with ancillary studies, such as complement IHC or IIF or ELISA of blister fluid in cases where pemphigoid is strongly suspected. Additionally, a repeat biopsy should be obtained if clinical suspicion for BP remains high due to potential for sampling error. If all study results remain negative, alternative diagnoses should be explored. Although we offer this algorithm as a potential guide, it is imperative that clinicians use both clinical reasoning and test findings to guide their overall decision-making.

IgE, eosinophils, and dermatoscopy were intentionally excluded from the algorithm because their role as standalone diagnostic markers remains inconclusive. A thorough drug history should be obtained in all patients to exclude drug-induced BP.

A comprehensive approach to diagnosing BP is essential. Although we offer a potential diagnostic algorithm, further research and standardization of diagnostic criteria are needed. Such measures will enhance the reliability of diagnostic modalities which in turn will improve the accuracy and efficiency of diagnosing this challenging disease and allow for earlier treatment.

Conflict of interest

Dr Prince Adotama has the following disclosures: consultant for Regeneron, Janssen, and Argenx; and investigator for Argenx. Dr Donna Culton has the following disclosures: Argenx, Advisory board; iCell, Consultant; Sanofi Genzyme, Advisory board; Sitala, Consultant; Regeneron, Consultant and Investigator; Cabaletta, Investigator; Incyte, Investigator and Stockholder; and Lilly, Investigator. All other authors have no conflicts of interest to declare.

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