Assessment of Diagnostic Strategy for Early Recognition of Bullous and Nonbullous Variants of Pemphigoid

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IMPORTANCE A substantial number of patients with bullous pemphigoid do not develop skin blisters and may not have received the correct diagnosis. Diagnostic criteria and an optimal diagnostic strategy are needed for early recognition and trials.

OBJECTIVES To assess the minimal requirements for diagnosis of bullous and nonbullous forms of pemphigoid and to evaluate the optimal diagnostic strategy.

DESIGN, SETTING, AND PARTICIPANTS This paired, multivariable, diagnostic accuracy study analyzed data from 1125 consecutive patients with suspected pemphigoid who were referred to the Groningen Center for Blistering Diseases from secondary and tertiary care hospitals throughout the Netherlands. Eligible participants were patients with paired data on at least (1) a skin biopsy specimen for the direct immunofluorescence (DIF) microscopy test; (2) indirect immunofluorescence on a human salt-split skin substrate (IIF SSS) test; and (3) 1 or more routine immunoserologic tests administered between January 1, 2002, and May 1, 2015. Samples were taken from patients at the time of first diagnosis, before introduction of immunosuppressive therapy, and within an inclusion window of a maximum of 4 weeks. Data analysis was conducted from October 1, 2015, to December 1, 2017.

MAIN OUTCOMES AND MEASURES Pairwise DIF, IIF SSS, IIF on monkey esophagus, BP180 and BP230 enzyme-linked immunosorbent assays, and immunoblot for BP180 and BP230 tests were performed. The results were reported in accordance with 2015 version of the Standards for Reporting Diagnostic Accuracy.

RESULTS Of the 1125 patients analyzed, 653 (58.0%) were women and 472 (42.0%) were men, with a mean (SD) age of 63.2 (19.9) years. In total, 343 participants received a pemphigoid diagnosis, with 782 controls. Of the 343 patients, 74 (21.6%, or 1 in 5) presented with nonbullous pemphigoid. The DIF microscopy was the most sensitive diagnostic test (88.3% [n = 303]; 95% CI, 84.5%-91.3%), whereas IIF SSS was less sensitive (77.0% [n = 263]; 95% CI, 72.2%-81.1%) but was highly specific (99.9%; 95% CI, 99.3%-100%) and complemented most cases with negative DIF findings. Results of the BP180 NC16A enzyme-linked immunosorbent assay did not add diagnostic value for initial diagnosis in multivariable logistic regression analysis of combined tests. These findings lead to the proposed minimal criteria for diagnosing pemphigoid: (1) pruritus and/or predominant cutaneous blisters, (2) linear IgG and/or C3c deposits (in an n-serrated pattern) by DIF on a skin biopsy specimen, and (3) positive epidermal side staining of IgG by IIF SSS on a serum sample; this proposal extends bullous pemphigoid with the unrecognized nonbullous form.

CONCLUSIONS AND RELEVANCE Both DIF and IIF SSS tests should be performed for diagnosis of the bullous and nonbullous variants of pemphigoid, and the BP180 NC16A enzyme-linked immunosorbent assay is recommended as an add-on test for disease activity monitoring.

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more than 20% of patients with bullous pemphigoid do not present with typical skin blistering, but with a pruritic nonbullous variant consisting of erythematous urticarial plaques, eczematous lesions, papules and nodules, or only excoriations. These patients with nonbullous pemphigoid may often have a misdiagnosis or be overlooked with a prolonged physician delay, especially in cases in which blisters never develop. Bullous pemphigoid is the most frequent subepidermal autoimmune bullous disease (sAIBD) and mainly affects older people. It is characterized by the presence of circulating IgG autoantibodies targeting the structural proteins BP180 and BP230 of the epidermal basement membrane zone. Annual incidence of bullous pemphigoid in Europe has increased substantially in the past decades, which might be attributed to an aging population, the availability of better diagnostic tests, and the recognition of patients with atypical clinical features.

Minimal diagnostic criteria for pemphigoid are needed but have not yet been established. Currently, the diagnosis is based on the typical presentation using combined clinical criteria to separate it from other pemphigoid diseases (such as mucous membrane pemphigoid, linear IgA disease, and epidermolysis bullosa acquisita), the histopathologic features of a subepidermal blister, and the detection of autoantibodies in a skin biopsy specimen by direct immunofluorescence (DIF) microscopy and in a blood sample by various immunoserologic tests. The 2015 European Dermatology Forum consensus recommendations require a positive DIF biopsy result for diagnosis, whereas the 2015 German guideline also allows diagnosis using various combinations of serologic tests. Studies suggest high diagnostic accuracies of commercially available enzyme-linked immunosorbent assay (ELISA) kits, but methodologic flaws may have led to an overestimation of the diagnostic accuracy in the intended population.

We evaluated the diagnostic accuracy of the DIF test on a skin biopsy specimen and various serologic tests in a paired study design involving a large cohort with suspected bullous or nonbullous pemphigoid. We then assessed the optimal diagnostic strategy by comparing the additional diagnostic value of combined diagnostic tests in multivariable logistic regression modeling, and we evaluated which tests should be performed for diagnosis at least (minimal requirements). Informed by these evaluations, we propose minimal diagnostic criteria for pemphigoid that support early recognition of this common cutaneous autoimmune disease.

Methods

Study Design and Participants

This single-center retrospective study was performed at the Groningen Center for Blistering Diseases, the national referral center for autoimmune bullous diseases in Groningen, the Netherlands. The study population consisted of consecutive patients with suspected pemphigoid from secondary and tertiary care hospitals throughout the Netherlands, including older people who had severe or refractory itch with or without skin blistering. Eligible participants were patients with paired data on at least (1) a skin biopsy specimen for the DIF test; (2) indirect immunofluorescence on a human salt-split skin (IF SSS) substrate test; and (3) 1 or more routine immunoserologic tests administered between January 1, 2002, and May 1, 2015. Samples were taken at the time of first diagnosis, before introduction of immunosuppressive therapy, and within an inclusion window of a maximum of 4 weeks. This study reports diagnostic tests in accordance with the Standards for Reporting Diagnostic Accuracy; see the eAppendix in the Supplement for a list of essential items for reporting diagnostic accuracy studies. According to national regulations in the Netherlands, this type of retrospective noninterventional study with leftover materials for diagnostic purposes does not require approval from the local medical ethical committee.

Reference Standard and Index Tests

No consensus reference standard for the diagnosis of pemphigoid was established. We used as a composite reference standard the criteria for diagnosis of the 2015 German S2k Guideline for diagnosis of bullous pemphigoid. Compatible clinical presentation of pemphigoid was defined as the presence of pruritus and predominant tense skin blisters or nonbullous skin morphologic features (not further specified). Results of direct immunofluorescence on a skin biopsy specimen were considered positive when linear or linear n-serrated-pattern deposits of IgG and/or C3c along the epidermal basement membrane zone were observed. The finding of indirect immunofluorescence on a human salt-split skin substrate (IF SSS) test was considered positive when epidermal side staining of IgG was observed. The clinical diagnosis of pemphigoid was made in the following cases: (1) compatible clinical presentation and a positive DIF finding, (2) compatible clinical presentation and a positive DIF finding as well as a positive IIF SSS result, (3) compatible clinical presentation and a positive IIF SSS finding as well as positivity in at least 1 other immunoserologic test (eg, immunoblot with reactivity to BP180 or BP230, IIF on monkey esophagus [ME] substrate, or BP180 or BP230 ELISA), and (4) compatible clinical presentation of tense blisters and a compatible histopathologic finding of subepidermal...
mal blister as well as a positive BP180 ELISA result and positivity in at least 1 other immunoserologic test (eg, immunoblot with reactivity to BP180 or BP230, IIF ME substrate, or BP230 ELISA).

Clinical features and test outcomes of cases with indeterminate or a single positive index test result were discussed among us, specifically by physicians (J.M.M. and M.F.J.), a pathologist (G.D.), and a biochemist (H.P.), to confirm a reject diagnosis of pemphigoid. Histopathologic data were not routinely analyzed in the study because histopathologic study is often nonspecific in nonbullous pemphigoid, does not enable differentiation of subtypes of pemphigoid diseases, and was not available in all cases.11 Excluded were participants with suspected mucous membrane pemphigoid as well as participants with a diagnosis of other autoimmune (bullous) diseases based on DIF findings and immunoserology results, including a linear u-serrated pattern (epidermolysis bullosa acquisita/bullous systemic lupus erythematosus), solely IgA depositions, or with IgG against autoantigens other than BP180 or BP230 (Figure 1). Diagnostic tests and assessments of the reference standard were separately performed.

Biopsy specimens for DIF were transported and stored mainly in saline solution (0.9% NaCl, overnight), liquid nitrogen, or Michel medium.17,18 Biopsy sites were defined in advance as (1) perilesional skin: erythematous nonbullous skin within 2 cm from a lesion; (2) lesional skin: bullous or nonbullous lesion except erosions; and (3) healthy skin: normal-appearing noninflamed skin from the inner aspect of upper arm. Seriation pattern analysis was assessed by routine DIF from 2009 onward using either a microscope with a 40× dry objective and 10× ocular lens, with a total magnification of ×400 (Leica DM2000 or LEICA DMRA; Leica Microsystems).17,19 The IIF SSS test was performed with a standard dilution of 1:8 (as described in the eMethods in the Supplement) on human substrate (from donated normal human skin tissue freshly obtained from routine reduction mammoplasty and abdominoplasty after signed informed consent) and validated with positive and negative controls.19 The routine multipstep immunoserologic test procedure included IIF on ME substrate, immunoblot with keratinocyte extract tested for IgG and IgA autoantibodies against BP180 and BP230,20 and commercially available BP180 NC16A (from 2007 onward) and BP230 (from 2009 onward) ELISA kits (Medical and Biological Laboratories Co) used according to the manufacturer’s protocol and with a positivity cutoff value of 9 U/mL or greater. Missing ELISA tests of patients with pemphigoid (n = 201) were performed post hoc.

Statistical Analyses

Data analysis was conducted from October 1, 2015, to December 1, 2017. We calculated diagnostic accuracy with the composite reference standard, including sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and diagnostic odds ratio (OR) according to standardized formulas and with 95% CIs. Sensitivities and specificities of paired diagnostic tests were compared using the McNemar test. The Mann-Whitney test, χ² test, or Fisher exact test was used to compare medians and proportions. Receiver operating characteristic curve analysis was used to determine the optimal cutoff value of continuous variables of autoantibody titer of BP180 NC16A and BP230 ELISAs by calculating maximum Youden J index values. With multivariable logistic regression modeling, we evaluated the additional diagnostic value of combined diagnostic tests (DIF, IIF SSS, and BP180 NC16A ELISA) for the initial diagnosis of bullous and nonbullous pemphigoid and included clinical variables (age, sex, pruritus, and blisters) with a backward selec-
Aim of this study was to retrospectively assess diagnostic performance of 15 selected laboratory tests in a large cohort of patients with suspected pemphigoid.

Table 1. Diagnostic Performance of Laboratory Tests in Study Participants With Suspected Pemphigoid

<table>
<thead>
<tr>
<th>Test</th>
<th>No. (With Pemphigoid/Controls)</th>
<th>% (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Diagnostic OR (95% CI)</th>
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<tbody>
<tr>
<td>Diagnostic Test</td>
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<tr>
<td>DIF</td>
<td>1125 (343/782)</td>
<td>88.3 (84.5-91.3)</td>
<td>99.2 (98.3-99.7)</td>
<td>98.1 (95.8-99.1)</td>
<td>95.1 (93.4-96.4)</td>
<td>115.1 (51.8-235.7)</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>IIF SSS</td>
<td>1125 (343/782)</td>
<td>77.0 (72.2-81.1)</td>
<td>99.9 (99.3-100.0)</td>
<td>99.6 (97.9-99.9)</td>
<td>90.8 (88.7-92.6)</td>
<td>601.9 (84.8-4271.3)</td>
<td>0.2 (0.2-0.3)</td>
</tr>
<tr>
<td>IIF ME</td>
<td>1077 (343/734)</td>
<td>57.1 (51.9-62.3)</td>
<td>98.8 (97.7-99.4)</td>
<td>95.6 (93.7-97.7)</td>
<td>83.1 (80.3-85.5)</td>
<td>46.6 (24.2-89.8)</td>
<td>0.4 (0.4-0.5)</td>
</tr>
<tr>
<td>Immunoblot</td>
<td>1093 (343/750)</td>
<td>70.3 (65.2-74.9)</td>
<td>94.7 (92.8-96.1)</td>
<td>85.8 (81.2-89.4)</td>
<td>87.4 (85.0-89.5)</td>
<td>13.2 (9.7-18.0)</td>
<td>0.3 (0.3-0.4)</td>
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<tr>
<td>ELISA</td>
<td></td>
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<tr>
<td>BP180 NC16A</td>
<td>904 (343/561)</td>
<td>70.0 (64.9-74.6)</td>
<td>89.8 (87.1-92.1)</td>
<td>80.8 (76.0-84.9)</td>
<td>83.0 (79.8-85.8)</td>
<td>6.9 (3.9-8.9)</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>BP230</td>
<td>774 (343/431)</td>
<td>44.6 (39.4-49.9)</td>
<td>92.8 (90.0-94.9)</td>
<td>83.2 (77.1-87.9)</td>
<td>67.8 (63.9-71.4)</td>
<td>6.2 (4.3-8.9)</td>
<td>0.6 (0.5-0.7)</td>
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<tr>
<td>Combined Tests</td>
<td></td>
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<tr>
<td>DIF + IIF SSS</td>
<td>1125 (343/782)</td>
<td>98.8 (97.0-99.7)</td>
<td>99.1 (98.2-99.6)</td>
<td>98.0 (95.9-99.0)</td>
<td>99.5 (98.7-99.8)</td>
<td>110.4 (52.2-230.9)</td>
<td>0.01 (0.00-0.03)</td>
</tr>
<tr>
<td>Bullous</td>
<td>456 (239/217)</td>
<td>98.3 (95.8-99.5)</td>
<td>99.5 (97.5-99.9)</td>
<td>99.6 (97.1-99.9)</td>
<td>98.2 (95.3-99.3)</td>
<td>213.4 (30.2-1508.0)</td>
<td>0.02 (0.01-0.04)</td>
</tr>
<tr>
<td>Nonbullous</td>
<td>600 (74/526)</td>
<td>100.0 (95.1-100.0)</td>
<td>98.9 (97.5-99.6)</td>
<td>92.5 (84.8-96.5)</td>
<td>100.0 (-)</td>
<td>87.7 (39.6-194.3)</td>
<td>0.00 (-)</td>
</tr>
<tr>
<td>DIF + ELISA</td>
<td>904 (343/561)</td>
<td>94.8 (91.8-96.9)</td>
<td>88.8 (85.9-91.3)</td>
<td>83.8 (80.3-86.7)</td>
<td>96.5 (94.6-97.8)</td>
<td>8.4 (6.7-10.7)</td>
<td>0.06 (0.04-0.09)</td>
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<tr>
<td>BP180 NC16A</td>
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<tr>
<td>Bullous</td>
<td>388 (239/149)</td>
<td>96.7 (93.5-98.5)</td>
<td>92.6 (87.2-96.3)</td>
<td>95.5 (92.2-97.4)</td>
<td>94.5 (89.7-97.2)</td>
<td>13.1 (7.4-23.1)</td>
<td>0.04 (0.02-0.07)</td>
</tr>
<tr>
<td>Nonbullous</td>
<td>460 (74/386)</td>
<td>86.5 (76.6-93.3)</td>
<td>87.3 (83.6-90.5)</td>
<td>56.6 (49.6-63.3)</td>
<td>97.1 (95.0-98.4)</td>
<td>6.8 (5.2-9.0)</td>
<td>0.15 (0.09-0.28)</td>
</tr>
</tbody>
</table>

Abbreviations: DIF, direct immunofluorescence microscopy; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; ME, monkey esophagus; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SSS, salt-split skin.

Results

Assessment of Diagnostic Strategy for Pemphigoid

From January 1, 2002, to May 1, 2015, we retrospectively analyzed data from 1125 patients with suspected bullous or nonbullous pemphigoid (Figure 1). Of the 1125 patients, 653 (58.0%) were women and 472 (42.0%) were men, with a mean (SD) age of 63.2 (19.9) years. Eventually, 343 participants (30.5%; mean [SD] age, 71.8 [7.4] years) received a pemphigoid diagnosis, compared with 782 controls (69.5%; mean [SD] age, 59.5 [19.7] years; P < .001). Of the 343 patients with a pemphigoid diagnosis, 74 (21.6%, or 1 in 5) presented with nonbullous pemphigoid. Table 1 summarizes the diagnostic accuracy of the DIF and immunoserologic tests.

Direct Immunofluorescence

The sensitivity of the index DIF test on a skin biopsy specimen (n = 303) was 88.3% (95% CI, 84.5%-91.3%), and the specificity was 99.2% (95% CI, 98.3%-99.7%). Solitary positive or inconclusive DIF findings were classified as false-positive in 6 participants (0.5%) in whom diagnosis of pemphigoid could not be confirmed, including chronic ulcers and a case of vasculitis. Twenty-one biopsy specimens for DIF contained artifacts with uninterpretable results and were excluded. Comparison of the biopsy sites for DIF of 1482 skin biopsy specimens showed that DIF on perilesional skin was most sensitive (90.4%; 95% CI, 85.7%-93.9%) and was superior to healthy skin (80.7%; 95% CI, 73.5%-86.5%; and lesion skin (76.2%; 95% CI, 65.7%-84.8%; P = .002) (Table 2). In the subgroup of participants without skin blisters (n = 788), DIF had a lower sensitivity of 81.1% (95% CI, 70.0%-88.9%), and no statistically significant differences were seen between biopsy sites (Table 2). In the 343 patients with pemphigoid, DIF detected immunodepositions of IgG in 277 biopsy specimens (91.4%), C3 in 223 (73.6%), and IgA in 83 (27.4%). In addition, DIF detected solely IgG deposition in 60 specimens (19.8%), combined presence of IgG and C3 in 135 specimens (44.6%), IgG and IgA in 20 specimens (6.6%), and combined IgG, C3c, and IgA in 62 specimens (20.5%). The DIF serration pattern analysis was routinely assessed in 728 consecutive cases from 2009 onward. The distinctive linear n-serrated pattern was observed in 138 of 181 cases (76.0%) with positive DIF, and the serration pattern was undetermined in the remaining cases (43 [24%]). No false-positive n-serrated patterns were observed.

Immunoserology

The sensitivity of the index IIF SSS test (n = 263) was 77.0% (95% CI, 72.2%-81.1%), and the specificity was 99.9% (95% CI,
DIF findings (10.5%; 95% CI, 5.9-18.8%) (Table 1). The IIF SSS test was complementary to DIF and showed a high sensitivity of 99.9% (95% CI, 99.3%-100.0%) (Table 1). Although IIF SSS had a statistically significantly lower sensitivity compared with DIF (77.0% vs 99.4%; P < .001), IIF SSS showed a high discriminative value of 2609.9 (95% CI, 2013.7-3280.8) (Table 1). The overlap in positivity of direct immunofluorescence on human salt-split skin (IIF SSS) substrate covering the near full circle represents the 98.8% of patients with pemphigoid. ELISA indicates enzyme-linked immunosorbent assay.

In patients with pemphigoid, ELISA detected mean (SD) serum concentrations of anti–BP180 NC16A of 48.8 (50.4) U/mL (eFigure 3 in the Supplement) and anti–BP230 IgG autoantibodies of 25.6 (35.0) U/mL (eFigure 5 in the Supplement) compared with 2.4 (9.3; range, 0-115 U/mL) U/mL and 1.5 (5.3; range, 0-50) U/mL in controls. Performance of combined ELISAs was 44.6% (95% CI, 39.9%-49.9%) at the cost of a lower specificity of 83.6% (95% CI, 79.8%-86.8%). Intending to use BP180 NC16A and BP230 in initial diagnosis and to prevent the high number of false-negative results.
null
sensitivity of 57% and was inferior to IIF SSS. Sensitivity of IIF might have been raised when IgG was specifically stained by a mixture of subclass specific antibodies (eg, IgG1, IgG4). Our results indicated that patients with nonbullous pemphigoid more often have BP230 as a target antigen and lower serum titers of autoantibodies against the immunodominant BP180 compared with patients with bullous pemphigoid. Patients with antibodies against BP230 often had significantly more negative DIF results, and the antibodies against BP230 contributed mainly to IIF positivity. A hypothesis is that antibodies against BP230 bind less to the intracellular target antigen in vivo in a skin biopsy specimen, but they bind to tissue sections of salt-split skin in vitro in which the BP230 antigen is exposed.

A meta-analysis of the BP180 NC16A ELISA (both commercial and in-house made) analyzed 17 studies with 538 patients with bullous pemphigoid and reported a pooled sensitivity of 87% and specificity of 98%, with the authors concluding that ELISA can be used as a diagnostic screening test in patients with autoimmune bullous diseases. In contrast, we report a low diagnostic performance for ELISA, which is in line with several reports by other investigators. Sensitivity and specificity vary with the cutoff chosen for ELISA and are not intrinsic to the test but critically dependent on the context of tested participants. Consequently, differences in study design and methodologic flaws of previous studies may have led to an overestimation of diagnostic test accuracy (eg, selection bias and spectrum bias with evident [bullous] disease and positive DIF or immunoserologic results), controls of healthy participants or blood donors not representative of the patient domain, variation of the reference standard, and a substantially lower number of participants. Commercially available ELISAs have a simple standardized readout, but to prevent the high number of false-positives, a substantially higher cutoff value would be needed, resulting in low sensitivities with no clinical use. Similar findings of a false-positive rate of 14.3% of the BP180 NC16A ELISA and a recommended higher positivity cutoff value have recently been reported in dermatology patients with suspected pemphigoid. Therefore, based on our findings, performing ELISA is recommended solely for monitoring relative disease activity in patients with confirmed pemphigoid instead of as an initial diagnostic test. Moreover, a survey in Germany indicated that DIF and IIF SSS were the most commonly used diagnostic tests, with the required expertise available in 98% (DIF) and 74% (IIF SSS) of university and nonuniversity hospitals.

The available clinical criteria for bullous pemphigoid are not applicable in patients with the nonbullous variant. Although histopathologic examination of a lesional skin biopsy specimen of a blister can support the diagnosis of bullous pemphigoid, it is neither sufficient nor essential for diagnosis and cannot distinguish between other subtypes of sAIBD. Moreover, histopathologic study is often nonspecific in nonbullous pemphigoid and indistinguishable from other inflammatory dermatoses.

These findings suggest that at least both DIF and IIF SSS tests should be performed for the diagnosis of pemphigoid. Subsequently, the minimal diagnostic criteria we propose for pemphigoid diagnosis consist of at least 2 positive results out of 3 criteria (2-out-of-3 rule): (1) pruritus and/or predominant cutaneous blisters, (2) linear IgG and/or C3c deposits (in an n-serrated pattern) by DIF on a skin biopsy specimen, and (3) positive epidermal side staining by IIF SSS on a serum sample. The minimal diagnostic criteria thus contradict that presence of blisters or a histopathologic finding is a prerequisite for diagnosing pemphigoid. To distinguish pemphigoid from other sAIBD, the predominance of cutaneous lesions opposes mucous membrane pemphigoid. The finding of a positive result DIF with linear IgG deposits with undetermined serration pattern along the basement membrane zone does not always imply a definitive diagnosis of pemphigoid. The required performance of an IIF SSS test excludes the subtypes of sAIBD with dermal side binding of autoantibodies: anti-p200 or laminin γ1 pemphigoid, epidermolysis bullosa acquisita or bullous systemic lupus erythematosus, and anti-laminin-332 mucous membrane pemphigoid. Linear IgA disease is excluded by the sole detection of the autoantibodies of IgA isotype and pemphigoid gestationis by the distinct patient population. Subtyping in seronegative patients requires routine DIF serration pattern analysis to identify the n-serrated pattern in pemphigoid, as opposed to the linear u-serrated pattern in epidermolysis bullosa acquisita.

The nosologic entity bullous pemphigoid, postulated 65 years ago by Lever, was adapted to simply pemphigoid in the United Kingdom to avoid redundancy. Therefore, we advocate the use of pemphigoid to encompass both the bullous and nonbullous variants of this cutaneous autoimmune disease that typically presents as a pruritic dermatosis in older people, with or without skin blistering.

Limitations
The limitation of this study is the absence of diagnostic criteria as a reference standard for the diagnosis of pemphigoid. A limitation of all studies of diagnostic accuracy is the inability to incorporate the results of analyzed tests.

Conclusions
We propose minimal diagnostic criteria that encompass the complete clinical spectrum of pemphigoid. These criteria also differentiate pemphigoid from other sAIBD.
Conflict of Interest Disclosures: None reported.

REFERENCES