Evaluation of Clinical Criteria for Diagnosis of Bullous Pemphigoid

Loic Vaillant, MD; Philippe Bernard, MD, PhD; Pascal Joly, MD, PhD; Catherine Prost, MD, PhD; Bruno Labelle, MD; Christophe Bedane, MD, PhD; Brigitte Arbeille, MD; Elisabeth Thomine, MD; Philippe Bertrand, MD; Catherine Lok, MD; Jean-Claude Roujeau, MD; for the French Bullous Study Group

Objective: To check the potential usefulness of clinical criteria for the diagnosis of bullous pemphigoid when state-of-the-art techniques such as Western immunoblotting, immunoprecipitation, and indirect immunofluorescence on salt-split skin or direct immunoelectron microscopy are not available.

Design: Comparison of the clinical criteria between 2 groups (with and without bullous pemphigoid) as defined by immunoelectron microscopy used as standard criterion, in a prospective study. Multivariate logistic regression analysis was carried out by including all items that were statistically significant (at P<.05 level) in univariate analysis.

Setting: Five dermatology departments in teaching hospitals.

Patients: The 231 patients studied had subepidermal autoimmune bullous diseases with linear IgG or C3 deposits in the basement membrane zone (157 with bullous pemphigoid, 33 with cicatricial pemphigoid, 30 with epidermolysis bullosa acquisita, 5 with lupus erythematosus, and 6 others). A second set of patients was used to calculate predictive values.

Results: The multivariate logistic stepwise analysis resulted in a final set of predictors that included only 4 items: absence of atrophic scars, absence of head and neck involvement, absence of mucosal involvement, and age greater than 70 years. No additional variables met the .05 significance level to enter into the model. If 3 of these 4 characteristics were present, a diagnosis of bullous pemphigoid could be made with a sensitivity of 90% and a specificity of 83%; these predictive values were calculated on a sample of 70 new cases.

Conclusions: With an estimated incidence of bullous pemphigoid among subepidermal autoimmune bullous diseases of 80%, the presence of 3 of the 4 significant criteria allows the diagnosis of bullous pemphigoid, with a positive predictive value of 95%. Our set of clinical criteria thus allows the diagnosis of bullous pemphigoid with good validity for both clinical practice and therapeutic trials.

Arch Dermatol. 1998;134:1075-1080

For editorial comment see page 1137

From the Department of Dermatology, Hôpital Trousseau, Tours, France (Dr Vaillant); Department of Dermatology, Hôpital Dupuytren, Limoges, France (Dr Bernard and Bedane); Departments of Dermatology (Dr Joly) and Pathology (Dr Thomine), Hôpital C. Nicolle, Rouen, France; Department of Dermatology, Hôpital Saint Louis, Paris, France (Dr Prost); Department of Dermatology, Hôpital H. Mondor, Créteil, France (Dr Roujeau); Department of Dermatology, Hôpital Sud, Amiens, France (Dr Labelle and Lok); and Departments of Electron Microscopy (Dr Arbeille) and Biostatistics (Dr Bertrand), Hôpital Bretonneau, Tours. Members of the French Bullous Study Group are listed on page 1079.

Bullous pemphigoid (BP), cicatricial pemphigoid (CP), herpes gestationis, epidermolysis bullosa acquisita (EBA), and vesiculobullous systemic lupus erythematosus (VBSLE) are subepidermal autoimmune bullous dermatooses (AIBDs) characterized by tense blisters arising on apparently normal skin or on an erythematous plaque and by linear deposits of IgG and/or C3 complement component. The blisters result from interaction of autoantibodies with the target antigens of the basement membrane zone (BMZ). In the last 15 years, considerable progress has been made in the comprehension of subepidermal AIBDs. The molecular basis of most of these disorders has been elucidated by using several new tools. Western immunoblotting and immunoprecipitation of epidermal extracts define the molecular weight of target protein antigens. The location of immune reactants can be determined by indirect immunofluorescence on salt-split skin and by immunoelectron microscopy (IEM). Target proteins have been cloned and their biochemical composition analyzed. Such progress has led to the general agreement that each AIBD should be defined according to the antigen that is the target of autoimmunity in each disease. For example, BP is currently defined by the detection of autoantibodies directed against 1 or 2 of the BP antigens (BPAG 1 and BPAG 2). The therapeutic approach to each subepidermal AIBD is somewhat different. In agreement with this concept, we believed at that time that such state-of-the-art techniques should be a prerequisite for including patients suffering from subepidermal AIBD in epidemiological or therapeutic clinical trials. Unfortunately it proved difficult to use these techniques in multicenter clinical trials.
PATIENTS AND METHODS

All patients who had newly diagnosed subepidermal autoimmune disease were included in this prospective study. They were examined in 5 departments of dermatology from 1983 to 1989. Criteria for enrollment were age greater than 18 years, presence of bullous dermatosis, subepidermal blister in hematoxylin-eosin examination of biopsy specimens, and presence of linear IgG or C3 deposits in the BMZ of perilesional skin detected by direct immunofluorescence. Pregnant women and patients who exhibited only IgA deposits in the BMZ were excluded. Clinical findings were prospectively recorded by means of the same standardized questionnaire that had been used in previous studies.14-16 Examination by IEM was performed by a previously described technique.17 Two hundred thirty-one patients met the inclusion criteria and had IEM examination. Thirty-three patients seen during the period of the study in our departments with inclusion criteria were not included in the study because of the absence of IEM examination; thus, the participation rate was 88% of all eligible patients seen during the period of the study.

CLINICAL CRITERIA

All patients were seen by one of us at the time of initial examination before initiation of treatment. The standardized clinical evaluation included pruritus; vesicles or blisters; milia; atrophic scars; traumatic blisters, defined as skin detachment induced by minimal trauma, such as Nikolsky sign in normal or perilesional skin; erythematous plaques; mucosal involvement; ungual involvement; and alopecia. Each item was evaluated immediately after enrollment and its presence or absence noted before initiation of treatment.

The localization of blisters was precisely analyzed: presence or absence on head, neck, trunk, and lower and upper limbs. These parts of the body were subdivided and presence or absence was noted in each localization (the trunk was divided into chest, abdomen, umbilicus, upper back, lower back, and buttocks).

The standardized clinical evaluation included other items, such as onset of pruritus and blisters, number of blisters, and percentage of body skin detachment, that were not selected as criteria for this study. The clinical assessment of the patients was always performed before the diagnosis was made.

LABORATORY CRITERIA

All patients had standard laboratory tests. For evaluation we used only eosinophilia and the presence or absence of circulating anti-BMZ antibodies detected by indirect immunofluorescence.

RESULTS

Two hundred thirty-one patients were included in the study. Mean age at diagnosis was 73.5 years. According to IEM findings, 157 patients (86 women and 71 men) were included in the BP group and 74 (32 women and
42 men) were included in the non-BP group. The mean (±SD) age was 73.5 (±16.0) years. In the non-BP group it was possible to diagnose the disease precisely in 70 of 74 patients. Thirty-three patients had CP; 24, inflammatory EBA; 8, chronic EBA; and 5, VBSLE.

The characteristics used as independent variables were age, presence of erythematous plaques, hypereosinophilia, anti-BMZ antibodies, absence of atrophic scar mucosal involvement, head and neck involvement, epidermal cysts, and mechanical blisters. For all these characteristics, subsequently used to determine a set of diagnostic criteria, the differences between the 2 groups were significant at \( P < .001 \), except for the criterion of anti-BMZ antibodies, which was significant at \( P = .01 \). The sensitivity and specificity of each characteristic were then determined (Table 1). We examined the ability of each item to predict the diagnosis of BP by univariate analysis (Table 1). The OR for the absence of atrophic scars was much higher than the ORs for other criteria (nearly 3 to 4 times higher).

The multivariate logistic stepwise analysis resulted in a final set of predictors that included only absence of atrophic scars, absence of head and neck involvement, absence of mucosal involvement, and age greater than 70 years. The equation of the logistic regression function was as follows: \( \logit (p) = 7.06 - 2.64 \text{ scar} - 1.046 \text{ head} - 1.08 \text{ mucosal} - 0.06 \text{ age} \). This stepwise multivariate analysis demonstrated that no additional variables met the .05 significance level to enter into the model (residual \( \chi^2 = 4.99; P = .42 \)), and thus no additional variables could significantly improve the ability to predict the diagnosis of BP. A set of diagnostic criteria was derived from this model, consisting of age greater than 70 years, absence of atrophic scars (ie, depressed scars), absence of mucosal involvement (ocular, nasal, oral, anal, or genital), and absence of head and neck blisters. We then tested this set of criteria on a new group of patients to test the hypothesis that 3 of 4 criteria allow the diagnosis of BP (\( \chi^2 = 97.5; P < .001 \)). The characteristics of the validation sample population were BP (n = 52) and non-BP (EBA, 3; CP, 15). The mean age was 77.5 (±13.9) years for patients with BP and 62 ± 23 years for the non-BP group.

Table 1. Sensitivity, Specificity, and Odds Ratio of Each Criterion for the Diagnosis of Bullous Pemphigoid*  

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No atrophic scars</td>
<td>91</td>
<td>70</td>
<td>23.8 (11.0-50.0)</td>
</tr>
<tr>
<td>No mucosal involvement</td>
<td>78</td>
<td>66</td>
<td>8.0 (4.1-15.4)</td>
</tr>
<tr>
<td>Age &gt;70 y</td>
<td>87</td>
<td>54</td>
<td>8.0 (3.7-16.7)</td>
</tr>
<tr>
<td>Erythematous plaques</td>
<td>87</td>
<td>51</td>
<td>7.1 (3.8-13.1)</td>
</tr>
<tr>
<td>No head and neck involvement</td>
<td>91</td>
<td>44</td>
<td>7.2 (3.7-14.0)</td>
</tr>
<tr>
<td>No milia</td>
<td>83</td>
<td>48</td>
<td>4.6 (2.4-8.5)</td>
</tr>
<tr>
<td>No mechanical blisters</td>
<td>90</td>
<td>32</td>
<td>4.5 (2.1-9.3)</td>
</tr>
<tr>
<td>Hypereosinophilia ((&gt;0.5 \times 10^9/L))</td>
<td>59</td>
<td>78</td>
<td>5.0 (2.6-9.8)</td>
</tr>
<tr>
<td>Anti-BMZ antibodies, No. positive</td>
<td>70</td>
<td>64</td>
<td>4.2 (1.8-9.7)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; BMZ, basement membrane zone.

Table 2. Performance of Suggested Set of Criteria for Diagnosis of Bullous Pemphigoid*  

<table>
<thead>
<tr>
<th>Prevalence, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>90</td>
<td>83</td>
<td>93</td>
<td>78</td>
</tr>
<tr>
<td>80</td>
<td>90</td>
<td>83</td>
<td>95</td>
<td>72</td>
</tr>
<tr>
<td>90</td>
<td>90</td>
<td>83</td>
<td>98</td>
<td>48</td>
</tr>
</tbody>
</table>

*PPV indicates positive predictive value; NPV, negative predictive value.

Subepidermal AIBDs are blistering diseases characterized by tissue-bound and circulating autoantibodies that are directed against a component of the cutaneous membrane zone; 4 of them (BP, CP, EBA, and VBLE) have linear de-
T he most important result in our study was obtained after the logistic procedure, which allowed us to retain only 4 criteria for the diagnosis of BP. These 4 criteria are different from the main criteria suggested by the literature and are not exactly the same as those suggested by the 4 higher ORs or higher relative values. The main difference from the literature is the importance of age. The most important difference from the results of ORs is that the presence of erythematous plaques, a very important criterion for the clinical description, does not increase the diagnostic value of our 4-criteria model. Indeed, the fact that no criteria other than age, absence of scarring, mucosal involvement, or head and neck involvement increase the diagnostic accuracy of BP is the major result of our study. This set was chosen to provide acceptable specificity and good sensitivity. If the presence of the 4 characteristics suggested by our model was required, very good specificity would be obtained but with poor sensitivity, and thus the requirement of the presence of the 4 characteristics would not be useful in practical routine. To estimate the predictive value of our proposed set of criteria, we calculated its positive and negative predictive values on a group of 70 new cases. On the hypothesis that our study reflects the usual features of subepidermal AIBD, this validation of the set of criteria demonstrated the good sensitivity (90%) with acceptable specificity (83%). To calculate any predictive value, the prevalence of the disease among the study population needs to be known. In a previous study15 we found that the mean annual incidence of subepidermal AIBDs in 3 French regions was 10.4 per million inhabitants. The prevalence of BP among subepidermal AIBDs (herpes gestationis and linear IgA dermatosis excluded) was between 80.5% and 82.6%. We can thus estimate that in nonpregnant adults with subepidermal AIBDs (ie, presence of blisters and positive direct immunofluorescence with C3 and/or IgG at the BMZ) the positive predictive value is between 93% and 98% (Table 2). Therefore, less
than 5% of the patients who fulfilled our suggested diagnostic criteria for BP had false-positive results. This seems acceptable both in clinical practice and for future therapeutic trials. A positive predictive value greater than 95% is acceptable because it allows inclusion of a few patients with AIBDs other than BP (in particular, a very few with EBA) in such a therapeutic trial and does not rule out too many patients. On the other hand, when a patient did not fulfill our set of diagnostic criteria, the probability that the patient really had non-BP disease was 50% to 78% (Table 2). The predictive value of our set of criteria suggests that a patient with fewer than 3 of the criteria (age less than 70 years, presence of atrophic scarring, mucosal involvement, head and neck blisters) might undergo further examinations if a precise diagnosis is needed to make a medical decision. In such cases, salt-split skin immunofluorescence could be helpful.

In conclusion, our study supports the usefulness of this set of diagnostic criteria for BP for diagnosing the individual case as well as for ensuring uniformity of groups of patients for clinical and therapeutic studies. The positive predictive value of salt-split skin immunofluorescence might be as good as that of our set of diagnostic criteria, and further studies are necessary to demonstrate this hypothesis.

References


23. Bhogal BS, Black MM. Diagnosis, diagnostic and research techniques. In: Woi...


