Clinical Diagnosis of Hypersensitivity Pneumonitis

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The diagnosis of hypersensitivity pneumonitis (HP) is difficult and often relies on histopathology. Our objective was to identify diagnostic criteria and to develop a clinical prediction rule for this disease. Consecutive patients presenting a condition for which HP was considered in the differential diagnosis underwent a program of simple standardized diagnostic procedures. High-resolution computed tomography scan and bronchoalveolar lavage (BAL) defined the presence or absence of HP. Patients underwent surgical lung biopsy when the computed tomography scan, BAL, and other diagnostic procedures failed to yield a diagnosis. A cohort of 400 patients (116 with HP, 284 control subjects) provided data for the rule derivation. Six significant predictors of HP were identified: (*1*) exposure to a known offending antigen, (*2*) positive precipitating antibodies to the offending antigen, (*3*) recurrent episodes of symptoms, (*4*) inspiratory crackles on physical examination, (*5*) symptoms occurring 4 to 8 hours after exposure, (*6*) and weight loss. The area under the receiver operating characteristic curve was 0.93 (95% confidence interval: 0.90–0.95). The rule retained its accuracy when validated in a separate cohort of 261 patients. The diagnosis of HP can often be made or rejected with confidence, especially in areas of high or low prevalence, respectively, without BAL or biopsy.

Keywords: lung diseases, interstitial; decision support techniques; probability

Hypersensitivity pneumonitis (HP) is a pulmonary disease with symptoms of dyspnea and cough resulting from the inhalation of an antigen to which the patient has been previously sensitized. Acute and subacute HP represent the most active forms of the disease, which may become chronic while remaining progressive. HP may also evolve to end-stage lung (1). The diagnosis of HP has most often relied on an array of nonspecific clinical symptoms and signs developed in an appropriate setting (2), with demonstration of interstitial markings on chest radiographs, serum precipitating antibodies against offending antigens, a lymphocytic alveolitis on bronchoalveolar lavage (BAL), and/or a granulomatous reaction on lung biopsies.

When considered separately, none of these findings has proved useful in the diagnosis of HP. It is accepted that 20% of chest radiographs are normal in acute cases (3). Many reports and reviews have challenged the diagnostic value of serum precipitins for case finding (4, 5). BAL can provide supportive elements in the diagnosis of the disease. A normal lymphocyte BAL count rules out all but residual disease (6), but an alveolar lymphocytosis is not specific to HP (7, 8). Transbronchial biopsies are of limited usefulness, even when granulomas are found (9). Also, HP gives a typical but nonspecific pattern on high-resolution computed tomograms (HRCT) (10).

Several groups have recommended diagnostic criteria for HP (11–13), without their diagnostic accuracy being tested. Consequently, we conducted a prospective multicenter cohort study of patients presenting with a suspected diagnosis of acute, subacute, or chronic HP. The objective was to develop a clinical prediction rule for diagnosis of active HP (that is a clinical tool that quantifies the contribution that various components of the history, physical examination, and basic laboratory results make toward the diagnosis in an individual patient [14]). Such a rule aims at helping clinicians to arrive at a more accurate estimate of probability of HP and to decide whether further investigation is needed to either rule in or rule out HP. Some of the results of this study have been previously reported in the form of an abstract (15).

METHODS

Patients

The HP study involved seven clinical sites from as many countries (*see* Appendix). Consecutive patients aged 18 years or older presenting with a pulmonary syndrome for which HP was considered in the differential diagnosis were included in the study. This cohort thus comprised patients with and without HP in a proportion that was unspecified *a priori*. We excluded patients with suspected Stage 1 sarcoidosis, those with a previous diagnosis of HP, and those referred for therapeutic evaluation of a known interstitial disease.

Diagnostic Criteria under Study

A review of the literature and consultations with content experts guided the development of a set of potential diagnostic criteria. These criteria included data usually collected during the initial investigation of patients with suspected HP (clinical history, physical examination, chest radiography marking patterns, pulmonary function tests, arterial blood gases, complete blood count, serum-precipitating antibodies). Other clinical characteristics unlikely to be found in HP (such as pleural effusion or serum antinuclear antibodies) were also considered, given their potential for making the diagnosis of HP less likely.

Attending clinicians systematically recorded the relevant data in every patient before making the final diagnosis. The symptoms and physical signs were recorded as present or absent on a standardized form during the initial clinical interview. The patients performed spirometry according to the American Thoracic Society requirements (16), lung volume measurement by plethysmography (17), and carbon monoxide diffusion capacity measurement by the single-breath method (18). The predicted values currently used within each laboratory were accepted. Arterial blood gases were measured while breathing room air. Partial pressure in oxygen was adjusted for altitude and reported as if it were obtained at sea level (19). The investigators tested for serum-precipitating antibodies in all patients using either the ELISA or the electrosyneresis methods

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(20) on a panel of antigens most likely to be encountered in their respective environments. The presence of antinuclear antibodies was tested by indirect immunofluorescent antibody staining of fixed cells (21). We reported precipitating antibodies and antinuclear antibodies as being either positive or negative according to center-specific predefined threshold values. Finally, the chest X-ray available at the time of the initial consultation was assessed.

Gold Standard

The investigators had to classify each patient as HP or non-HP. In the absence of a unique gold standard defining the presence or absence of HP, the final diagnosis relied on findings of BAL, HRCT, and, if needed, other diagnostic procedures. BAL lymphocytosis ($\geq$ 30% for non- and exsmokers and $\geq$ 20% for current smokers [22]) and bilateral ground-glass or poorly defined centrilobular nodular opacities on HRCT (10) were required for a diagnosis of HP to be accepted without resorting to additional diagnostic procedures. When the association of HRCT and BAL did not allow the investigators to arrive with confidence at a final diagnosis of HP or non-HP, the decision regarding additional procedures (including for instance BAL fluid cytology or culture, transbronchial or endobronchial biopsy, or mediastinoscopy) was not protocol-based but left to the investigators, according to clinical circumstances and their usual practice. Patients underwent surgical lung biopsy when the HRCT, the BAL, and other diagnostic procedures failed to yield a diagnosis. Pathologic criteria of HP included chronic inflammatory infiltrates along small airways, diffuse interstitial infiltrates of chronic inflammatory cells, and scattered, small, nonnecrotizing granulomas (23). In the case where a patient was classified as non-HP, a specific diagnosis was not mandatory, provided that HP was definitely excluded on the basis of BAL. Patients with inactive, late emphysematous, or fibrotic sequelae of HP were classified in the control group.

Adjudication committee. Four clinicians, one pathologist, and one radiologist were responsible for ascertaining the final diagnoses that were submitted by the clinical centers. The clinical committee first reviewed each case for data consistency with the investigator's final diagnosis and could request any additional information (such as data from the initial investigation or follow-up). Disagreement between the submitting center and the clinical adjudication committee led to a reassessment of the HRCT and, when available, biopsy material by a radiologist and a pathologist who were unaware of the submitted diagnosis. In addition to providing, when possible, a specific diagnosis from the HRCT or biopsy material, both classified each case as probable HP, indeterminate, or probable non-HP. The committee accepted the clinical diagnosis if (*1*) both the radiologist and the pathologist agreed with the clinical diagnosis or (*2*) the pathologist could provide the same specific diagnosis as the one submitted by the clinical center. The committee overturned the clinical diagnosis if (*1*) both the radiologist and the pathologist disagreed with the clinical diagnosis or (*2*) the pathologist could provide a specific diagnosis (different from the submitted one).

Statistical Analysis

Derivation of the prediction rule. In this analysis, we sought to reduce the list of potential diagnostic criteria to those that would recognize a

TABLE 1. DISTRIBUTION OF DIAGNOSES

	No. of Patients	
Diagnosis	Derivation Cohort	Validation Cohort
Patients with HP	116	83
Pigeon breeder's/bird fancier's disease	71	61
Farmer's lung	25	13
Humidifier lung	3	0
Suberosis	2	0
Summer-type HP	2	0
Various exposures to fungi	11	8
HP of unknown origin	2	1
Control subjects	284	178
Idiopathic interstitial pneumonia*	132	94
Sarcoidosis	35	17
Interstitial disease associated with collagen vascular disease	24	11
Drug-induced pulmonary disease	18	8
Bronchiolitis obliterans (with or without organizing pneumonia)	15	10
Unspecified interstitial lung disease†	15	11
Infectious pneumonia	4	7
Histiocytosis X	8	2
Asthma	5	1
Silicosis	5	0
Eosinophilic pneumonia	4	1
Normal lung	4	0
Bronchoalveolar carcinoma/carcinomatous lymphangitis	0	4
Residual HP‡	2	1
Organic dust toxic syndrome	1	2
Lymphocytic interstitial pneumonia	1	1
Pulmonary edema (heart failure)	1	1
Radiation pneumonitis	0	2
Miscellaneous	9§	4‖
Total	400	261

Definition of abbreviation: HP = hypersensitivity pneumonitis.

* Includes patients with a clinical diagnosis of idiopathic pulmonary fibrosis and those with pathologic diagnoses of usual, desquamative, respiratory bronchiolitis and acute and nonspecific interstitial pneumonia (28).

† Includes patients in whom no specific diagnosis could be reached but in whom HP was excluded on the basis of bronchoalveolar lavage.

‡ Late emphysematous or fibrotic sequelae of HP in which the typical alveolar lymphocytosis of active HP has disappeared.

§ Includes single cases of alveolar hemorrhage, anthracosis, berylliosis, Churg–Strauss syndrome, diffuse panbronchiolitis, hepatopulmonary syndrome, human immunodeficiency virus–associated nonspecific interstitial pneumonia, necrotizing sarcoid granulomatosis, and pulmonary amyloidosis.

‖ Includes single cases of alveolar proteinosis, crack lung, *Pneumocystis carinii* pneumonia, and Wegener's granulomatosis.

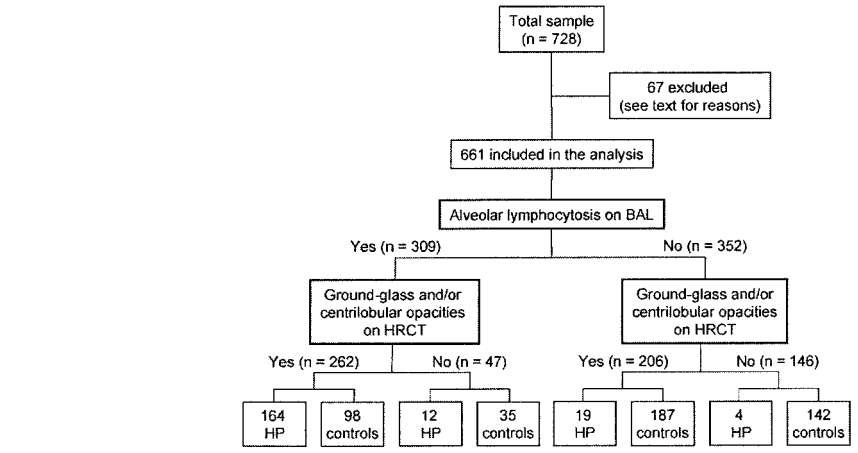

Figure 1. Diagram illustrating each step in the patient classification process according to their bronchoalveolar lavage (BAL) and high-resolution computed tomography findings. Within each group, the mean percentage of lymphocytes on BAL (± SD) is given for both patients with hypersensitivity pneumonitis (HP) and patients without HP (*see* text for the definition of alveolar lymphocytosis). Also, the proportion of patients submitted to surgical lung biopsy, transbronchial biopsy, and other tests is provided. Other procedures included BAL fluid cytology or culture, mediastinoscopy, and endobronchial, lymph node, or skin biopsies. Patients may have been submitted to more than one additional procedure.

high proportion of patients with HP and exclude a high proportion of patients with other diseases (24). We first compared the clinical characteristics of the patients in the HP and non-HP groups using two-tailed Fischer's exact and unpaired *t* tests for dichotomous and continuous variables, respectively. From this analysis, we incorporated the variables found significant at the 0.05 level in a stepwise logistic regression model. Odds ratios and 95% confidence intervals (CI) for the multivariate predictors were identified. We then constructed a receiver operating characteristic (ROC) curve (that is a plot of the true-positive vs. false-positive rates of HP at various thresholds of probability) using the predicted probabilities of HP from the logistic regression analysis as diagnostic tests for HP. Also, we computed the area under the ROC curve, which indicates the probability that a random pair of HP and non-HP patients will be correctly classified as to their disease state (25).

Validation. We prospectively validated the rule using a separate cohort of patients that met the same inclusion criteria as those included in the development phase of the study. During the phase of validation, the investigators were kept blind to the criteria identified during the derivation phase and were asked to collect the same data. In this analysis, the model developed in the derivation phase of the study was evaluated by comparing the areas under the ROC curve (25). The hypothesis that the observed proportion of patients with HP was different from the predicted proportion in both the derivation and the validation cohorts was tested using the goodness-of-fit statistic described by Lemeshow and Hosmer (26). Finally, we constructed calibration curves, which are plots of the observed probability of HP compared with the predicted probability of HP ordered by the increasing probability of the disease (27).

In secondary analyses, to verify whether the rule can be applied in different settings, we cross-validated it by comparing, within each clinical site, the classification of each patient with their actual status. Also, to investigate the potential bias introduced by the use of information overlapping the criteria under study to define the presence or absence of HP, we constructed ROC curves using the subsets of patients who were submitted to surgical lung biopsy and those who were not.

Probability of HP. The clinical prediction model yielded an equation expressing the probability of HP as a function of the statistically significant variables. From this equation, we constructed a table of probability for combinations of predictors.

RESULTS

Patients

Between February 1998 and September 2001, 728 patients were enrolled. Of these, 67 (9%) were excluded from the analysis by the adjudication committee for the following reasons: unavailable or uninterpretable BAL (n = 49) or HRCT (n = 9); inconsistent final diagnosis that could not be ascertained (n = 7); and Stage 1 sarcoidosis (n = 2). Thus, 661 patients (56% women; mean age: 55 years; standard deviation: 14) contributed to the analysis. The data from the first 400 patients (116 HP, 284 non-HP) were used to develop the prediction rule, whereas those of the next 261 patients (83 HP; 178 non-HP) were used to validate it. The distribution of the final diagnoses is summarized in Table 1. A surgical lung biopsy supported the final diagnosis in 73 patients (37%) with HP and in 156 patients (34%) without HP. The clinical adjudication committee resorted to the expertise of the radiologist and/or the pathologist for 89 cases: 78 HRCT and 60 biopsies were reviewed. The adjudication committee overturned the submitted diagnosis in only 17 patients (3%). Figure 1 details each step of the patient classification process according to their BAL and HRCT findings.

Derivation of the Prediction Rule

From the 18 variables that reached the level of statistical significance in the univariate analyses comparing the HP and non-HP groups (Table 2), we excluded Po_2 because the absolute difference fell within the precision range of the test (29). The logistic regression model identified six significant predictors of HP: (*1*) exposure to a known offending antigen, (*2*) positive precipitating antibodies to the offending antigen, (*3*) recurrent episodes of symptoms, (*4*) inspiratory crackles on physical examination, (*5*) symptoms occurring 4 to 8 hours after exposure, and (*6*) weight loss (Table 3). The area under the ROC curve (Figure 2) was 0.93 (CI: 0.90–0.95). We determined that the threshold producing the most appropriate trade-off between sensitivity and specificity was a probability of HP of 45%. At this point of the ROC curve, the sensitivity of the rule was 86% (95% CI: 0.79–0.92) and its specificity, 86% (95% CI: 0.81–0.90).

Validation

Applying the rule to the 261 patients in the prospective validation cohort, the area under the ROC curve was 0.90 (CI: 0.87–0.94) and was not statistically different from the area obtained in the derivation phase (p = 0.32). The goodness-of-fit statistics for the derivation (χ^2 = 10.04; degrees of freedom = 7; p = 0.2)

TABLE 2. POTENTIAL PREDICTORS OF HYPERSENSITIVITY PNEUMONITIS

Criteria	Patients with HP	Control Subjects	p Value
Clinical symptoms/history			
Exposure to antigens	97%	33%	< 0.001
Dyspnea	98%	86%	< 0.001
Cough	91%	75%	< 0.001
Chills	34%	14%	< 0.001
Tightness of chest	35%	20%	0.002
Weight loss	42%	25%	< 0.001
Body aches	24%	14%	0.018
Wheezing	31%	11%	< 0.001
Chest (pleuritic) pain	10%	5%	0.040
Symptoms 4–8 h after exposure	27%	2%	< 0.001
Recurrent episodes of symptoms	44%	12%	< 0.001
Smoking status: current smoker	6%	20%	< 0.001
Physical signs			
Fever	19%	7%	0.001
Inspiratory crackles	87%	72%	0.002
Wheezing	16%	10%	0.06
Cyanosis	32%	21%	0.030
Clubbing	21%	27%	0.21
Supraclavicular or cervical adenopathies	3%	4%	0.76
Laboratory			
Blood work			
Positive precipitins to known antigens	78%	31%	< 0.001
P_{O_2}, mm Hg	70	74	0.001
White blood cell count, $\times 10^9$/L	7.7	7.9	0.61
Lymphocytes	29%	26%	0.22
Eosinophils	3%	4%	0.54
Positive antinuclear antibodies	19%	23%	0.43
Pulmonary function testings, % predicted value			
FEV_1	73%	74%	0.67
FEV_1/FVC	101%	102%	0.52
Carbon monoxide diffusion capacity	62%	68%	0.06
Functional residual capacity	96%	91%	0.14
Total lung capacity	82%	81%	0.61
Chest X-ray			
Normal chest X-ray	14%	5%	0.007
Basal markings	41%	50%	0.19
Pleural effusion	1%	2%	0.68
Hilar/mediastinal lymphadenopathies	3%	7%	0.10

For definition of abbreviation *see* Table 1.
Results are given as the percentage of patients presenting each variable in both groups (patients with HP vs. control subjects).

and validation ($\chi^2 = 4.30$; degrees of freedom = 7; p = 0.7) data sets indicated that the observed proportion of patients with HP was similar to the predicted proportion in both the derivation and validation groups. The calibration curves for the derivation and validation data sets demonstrated good calibration of the prediction rule (Figure 3).

The rule was associated with similar operating characteristics across the seven clinical sites, the area under the curve ranging from 0.83 to 1.00 (median: 0.93). The accuracy of the rule was less in the subgroup of patients who were submitted to surgical lung biopsy (area under the curve: 0.83; CI: 0.78–0.98) than in the subgroup of those who were not (area under the curve: 0.95; CI: 0.92–0.97; p = 0.001).

Probability of HP

The probability of HP computed for each of the 64 (2^6) combinations generated by the six significant predictors of HP is presented in Table 4.

DISCUSSION

Interstitial lung diseases often pose diagnostic challenges, even to expert clinicians. Recent studies emphasized that additional

TABLE 3. SIGNIFICANT PREDICTORS OF HYPERSENSITIVITY PNEUMONITIS

Variables	Coefficient	Odds Ratio	Confidence Interval
Intercept	−6.57	–	–
Exposure to a known offending antigen	3.66	38.8	11.6–129.6
Positive precipitating antibodies	1.68	5.3	2.7–10.4
Recurrent episodes of symptoms	1.20	3.3	1.5–7.5
Inspiratory crackles	1.51	4.5	1.8–11.7
Symptoms 4–8 h after exposure	1.97	7.2	1.8–28.6
Weight loss	0.70	2.0	1.0–3.9

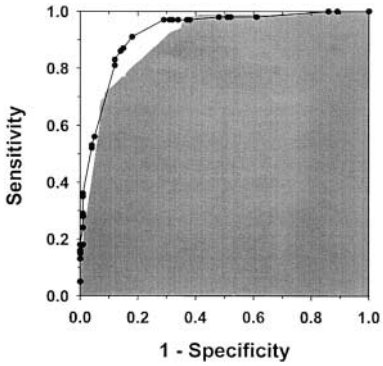

Figure 2. Receiver operating characteristic (ROC) curve for the prediction rule. The probability of HP derived from the model can be considered as a diagnostic test, and the trade-off between sensitivity and specificity at various thresholds of the probability of HP is given by the ROC curve. *Dotted line* indicates derivation cohort; *shaded area* indicates validation cohort.

investigations (including surgical biopsy) are indicated in patients with interstitial diseases in whom the diagnosis remains unclear after initial assessment (30, 31). The results of the HP Study indicated that a simple clinical prediction rule may guide clinical practice by providing estimates of the probability of acute, subacute, or chronic progressive HP from noninvasive testing. The predictors of HP we identified do not apply to chronic and inactive forms of the disease.

The best diagnostic strategy will then depend on the probability of HP. For instance, in a farmer presenting with recurrent episodes of respiratory symptoms and inspiratory crackles and testing positive for the corresponding precipitating antibodies, the probability of HP would be 81% (Table 4). Another patient presenting with progressive dyspnea and inspiratory crackles as the only criteria of HP would have a probability of HP of less than 1%. Further investigation would be mandated in the former. The typical findings of an alveolar lymphocytosis and/or bilateral ground-glass opacities on HRCT in the former patient would confirm the diagnosis of HP, without resorting to surgical lung biopsy. However, HP would be confidently ruled out in the latter and the investigation oriented elsewhere. We submit that a probability greater than or equal to 90% or less than or equal to 10% should be sufficient in most cases to, respectively, rule in or rule out HP, especially in areas of high or low prevalence of HP, respectively. However, the "test threshold" (that is the probability below which a clinician would dismiss the diagnosis and order no further test) and the "treatment threshold" (that is the probability above which a clinician could consider the diagnosis confirmed and would stop testing) are likely to differ according to the clinical implications of the diagnosis (32, 33). A clinician and his/her patient will be more likely to accept the diagnosis of bird fancier's disease when the offending antigen is a pet, even if the probability of HP is 75%. In such a case, antigen avoidance would be appropriate. Further investigation would be required only if the clinical course is unusual. On the other hand, a clinician and his/her patient will want to confirm the diagnosis of farmer's lung even if the probability of HP is around 90%, given that more than 50% will quit farming within 6 years of a diagnosis of farmer's lung (34).

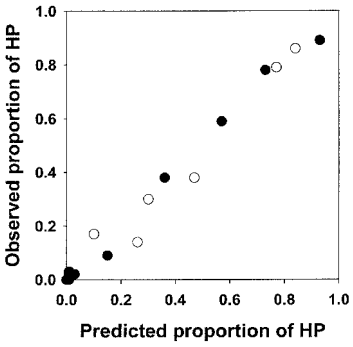

Figure 3. Calibration curves for the prediction rule. Patients were grouped by decile of the predicted probability of HP. The calibration curves display the observed proportion of HP versus the predicted proportion for each decile. *Solid circles* indicate derivation data; *open circles* indicate validation data.

Some of our findings deserve further attention. First, the enrollment of patients without interstitial disease stemmed from the inclusion criteria of the study: all patients presenting with a pulmonary syndrome for which active HP was considered were eligible. A typical example was the inclusion of patients (often farmers) who presented with recurrent episodes of dyspnea in whom the investigation ruled out HP and demonstrated asthma. Similarly, in four patients who presented with symptoms suggestive of HP, we could not demonstrate any lung disease. Second, the identification of a potential offending antigen is crucial for the clinical diagnosis of HP. Inquiry about occupational and home environmental exposures will most often uncover the cause of the disease. In rare instances (1.5% of our cohort), the diagnosis of HP was made without any identifiable offending antigen. In these cases, the diagnosis was supported by the careful exclusion of other causes of BAL lymphocytosis and typical findings of HP on lung biopsy. Third, although smoking is often thought of as having a protective effect against the development of HP (35), nonsmoking was not identified as an independent predictor of HP.

An important strength of the HP Study was its adherence to methodologic standards for both the derivation and the validation of the rule (14, 36). The patients were chosen in an unbiased fashion and represented a wide spectrum of diseases from a variety of institutions, hence increasing generalizability. We included all perceived important predictors, and those of significance were present in a large proportion of the study population. The predictors and outcomes were clearly defined. In the absence of a unique gold standard defining HP, every effort was made to properly classify each patient as either HP or non-HP independent of the criteria under study. The final diagnosis relied on the combination of typical findings on BAL and HRCT and the exclusion of competing diagnoses. Surgical lung biopsy was available in 35% of the patients. An adjudication committee reviewed every case for consistency. We submitted the difficult cases to further investigation, including clinical reassessment providing follow-up information and a blind and independent review of the HRCT and biopsy material when available. The accuracy of the rule being less in patients who were submitted to surgical lung biopsy than in those who were not does not necessarily indicate bias due to circularity. This may result from the fact that only the most difficult cases were submitted to surgical lung biopsy. Finally, considering an estimated annual incidence of interstitial lung disease of approximately 30 per 100,000 (37), the sample size was large and determined *a priori*. The derived rule made clinical sense because it matched the expected typical findings in HP.

Potential applications of prediction rules include periodic surveillance in high-risk workers or case finding in outbreaks of HP. Several rules have been developed for such purposes (38–40). Little information is available regarding their accuracy. Whether the rule we developed can be used for case finding of HP remains uncertain. Because "exposure to a known offending antigen" is the strongest predictor of HP in our cohort of patients presenting with a variety of interstitial lung diseases (Table 3), our rule may not retain its discriminative properties when used in a homogeneous population of workers, all of whom have been exposed to a common antigen.

Much confusion still surrounds the classification of HP. Its clinical presentations have classically been defined as acute, subacute,

TABLE 4. PROBABILITY OF HAVING HYPERSENSITIVITY PNEUMONITIS

				Crackles, %			
				+		−	
				Serum Precipitins		Serum Precipitins	
Exposure to a Known Offending Antigen	Recurrent Episodes of Symptoms	Symptoms 4–8 h After Exposure	Weight Loss	+	−	+	−
+	+	+	+	98	92	93	72
+	+	+	−	97	85	87	56
+	+	−	+	90	62	66	27
+	+	−	−	81	45	49	15
+	−	+	+	95	78	81	44
+	−	+	−	90	64	68	28
+	−	−	+	73	33	37	10
+	−	−	−	57	20	22	5
−	+	+	+	62	23	26	6
−	+	+	−	45	13	15	3
−	+	−	+	18	4	5	1
−	+	−	−	10	2	2	0
−	−	+	+	33	8	10	2
−	−	+	−	20	4	5	1
−	−	−	+	6	1	1	0
−	−	−	−	3	1	1	0

All the predictors are dichotomous variables: '−' indicates absent; '+' indicates present.

and chronic (12). The distinction between acute and subacute HP is often difficult as both likely represent different manifestations of a single disease that may be related more to the pattern of antigen exposure than to the offending antigen itself. This statement is supported by our finding of considerable overlap in the clinical manifestations of patients with farmer's lung (usually considered as the prototype of acute HP) and those with pigeon breeder's or bird fancier's diseases (the prototypes of subacute and chronic HP, respectively; data not shown). Also, chronic HP may still be active and progressive. Others have suggested a classification that takes into account the progression of the disease (acute intermittent, acute progressive, chronic progressive, chronic nonprogressive) that can be assessed only retrospectively (1, 41). For practical purposes, we suggest that patients with HP be considered as having either active or residual disease, the latter representing late emphysematous or fibrotic sequelae of the disease in which the typical alveolar lymphocytosis of active HP has disappeared.

The potential implications of such a simple rule are numerous. These simple criteria may establish uniformity in the definition of HP. By quantifying the individual contributions of various components of the history, physical examination, and basic laboratory results, the rule may reduce the number of unnecessary invasive procedures (including BAL or surgical lung biopsy) in patients with typical presentation of the disease. It may also rule out HP with confidence in those with low clinical scores. However, the HP Study will prove useful only if it increases awareness about HP and it can be used by others in various settings with confidence in its accuracy (36).

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APPENDIX: THE HP STUDY GROUP

Protocol Development

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Clinical Sites

Mexico (212 patients)—Instituto Nacional de Enfermedades Respiratorias, Mexico DF: Moises Selman, M.D., Andrea Estrada, M.D., Mayra Mejia, M.D., Teresa Suarez, M.D., Miguel Gaxiola, M.D., Guillermo Carrillo, M.D., Julio Robledo, M.D. Germany (123 patients)—Ruhrlandklinik, Essen: Ulrich Costabel, M.D., Norio Satake, M.D., Ricarda Cziborra, M.D., Josune Guzman, M.D. Canada (98 patients)—Hôpital Laval, Université Laval, Quebec, Quebec: Yvon Cormier, M.D., Gétane Bédard, R.N., Diane Page, R.N., Evelyne Assayag, M.Sc. France (90 patients)—Centre Hospitalier Universitaire de Besançon, Besancon: Jean-Charles Dalphin, M.D., Gabriel Reboux, Ph.D. Japan (55 patients)—Kumamoto University School of Medicine, Kumamoto: Masayuki Ando, M.D., Hisato Yamasaki, M.D. Spain (49 patients)—Hospital Universitari Vall d'Hebron, Barcelona: Ferran Morell, M.D., Leonardo Reyes, M.D. Finland (34 patients)—Kuopio University Hospital, Kuopio: Riitta Erkinjuntti-Pekkanen, M.D., Ph.D.

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Data Management

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Analysis

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