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# Utility of precipitating antibody testing in the diagnostic evaluation of chronic hypersensitivity pneumonia

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**Abstract.** *Background:* Chronic hypersensitivity pneumonitis (HP), in its progressive fibrotic form, is difficult to distinguish from other fibrosing interstitial lung diseases (ILD), particularly idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP). The role of serum precipitating antibodies in the diagnosis of fibrosing ILD has not been discussed in recent clinical practice guidelines. *Objectives:* The aim of this study is to assess the role of precipitins in the diagnosis of non pre-selected cases of fibrosing ILD. *Methods:* Clinical records of 108 consecutive patients referred for presumptive fibrosing ILD to our institution were retrospectively assessed for exposure history, serum precipitins, other diagnostic examinations, and multidisciplinary diagnosis (MDD). Their high resolution computed tomography (HRCT) images were blindly and prospectively re-assessed. We estimated sensitivity and specificity of precipitins against MDD and, to account for incorporation bias, we used two composite reference standards (CRSs), having exposure history and HRCT as component tests. *Results:* Definitive diagnosis achieved through MDD were chronic HP (17% of cases), NSIP (42%), IPF (18%) and others (23%). For serum precipitins, we estimated a sensitivity of 72% and a specificity of 68% using MDD as the reference standard. Sensitivity against the AND-CRS was 55%, while specificity against the OR-CRS was 61%. On the basis of this results, we can expect true sensitivity of precipitins lying between 55 and 72% and specificity between 61 and 68%. *Conclusions:* Serum precipitating antibodies did not result as having a relevant role in the diagnostic approach to chronic HP *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 149-155)*

**Key words:** interstitial lung disease, hypersensitivity pneumonia, precipitins, idiopathic pulmonary fibrosis

## Introduction

Differential diagnosis in the wide and heterogeneous group of fibrosing interstitial lung diseases (ILD) is complex. The diagnosis of chronic hypersensitivity pneumonitis (HP) is particularly challenging, due to the absence of standardised and validated diagnostic criteria (1) and the fact that advanced stages are often indistinguishable from idiopathic pulmonary fibrosis (IPF), fibrotic non-specific interstitial pneumonia (NSIP), and fibrosing sarcoidosis (2).

Chronic HP is the result of an immunologically induced inflammation of lung parenchyma in response to the exposure to a variety of inhaled organic antigens. However, despite an accurate exposure history, the inciting antigens may not be identifiable in some patients (3). Precipitins, i.e. serum precipitat-

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ing antibodies, produced during the immunologic reaction against the offending antigens are considered good indicators of exposure, and were included in the diagnostic criteria proposed by Schuyler (4) and the HP Study Group (5). Even though their absence does not rule out HP, it has been suggested that precipitins can be helpful in differentiating chronic HP from other fibrosing ILD (4,5). However, the most recent guidelines for diagnosis and management of IPF do not mention the use of serum precipitins in the diagnostic work up of fibrosing ILD (6).

This retrospective study aimed to evaluate the role of serum precipitating antibodies in the diagnostic management of non pre-selected cases of fibrosing ILD.

## Methods

### *Population and diagnostic tests*

The study was conducted retrospectively on a total of 108 consecutive patients referred for presumptive fibrosing ILD to the outpatient clinic of the Respiratory Medicine Department, San Gerardo Hospital, Monza, Italy, from October 2008 to September 2011. The study was approved by the San Gerardo Hospital Institutional Review Board, Monza, Italy (approval number 1196).

Paper and electronic clinical records of all patients were assessed for occupational, domestic and recreational exposure to organic inhaled antigens known to be associated to the development of HP, respiratory symptoms (episodic, exertional or resting dyspnoea, dry or productive cough, thoracic pain or discomfort), and systemic symptoms (low-grade fever, arthralgia, weight loss).

A high resolution computed tomography (HRCT) scan, performed within 6 months from the first visit, was examined by a radiologist (N.S.) of recognized experience in thoracic imaging blinded to any clinical, functional and laboratory data. He offered a first and a second diagnostic hypothesis, indicating also a percentage of diagnostic confidence. The hypothesis with a confidence ≥ 60% was considered as the first diagnostic hypothesis, while the one ≤ 40% as the second.

All patients were evaluated for serum precipitating antibodies using the Immulite 2000 Immunoassay Analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, USA) available at the Clinic Immunologic Laboratory of our institution. The commercial antigenic panel tested included Penicillum Notatum, Aspergillus Fumigatus, Alternaria Alternata, Aspergillus Niger, Saccharopolyspora rectivirgula *(formerly* Micropolyspora faeni) and pigeons' excrements. As recommended by the test provider, normal values were lower than 30 mg/l for moulds and lower than 55 mg/l for pigeons' excrements.

Bronchoscopy and bronchoalveolar lavage (BAL) were performed as part of the clinical evaluation in 52 patients. Three repeated samples of 50 ml of room temperature sterile physiologic saline were instilled through the bronchoscope and retrieved by gentle mechanical suction. Cells in the fluid were collected by cytocentrifugation and slides were stained with May-Grunwald-Giemsa stains. The total number of alveolar macrophages, lymphocytes, mastocytes, red blood cells was determined by counts of at least 200 cells in random fields at 400X (Olympus, Japan). BAL lymphocytosis was considered suggestive for chronic HP if lymphocytes in differential cell count was higher than 30% (7).

In all patients, a definitive diagnosis was reached through multidisciplinary diagnosis (MDD), as endorsed by guidelines (6) and usually performed at our institution.

### *Statistical methods*

In our retrospective cohort, surgical lung biopsy was available only for a minority of patients. Thus, to assess the diagnostic accuracy of precipitins in non pre-selected cases of fibrosing ILD, we used MDD as the reference standard. However using MDD, which already included precipitins results, as the reference test, leads to an overestimation of the diagnostic accuracy of the test under evaluation (incorporation bias) (8). Therefore, to assess precipitins' diagnostic accuracy, we also used a composite reference standard (CRS), i.e. a pre-defined rule to make a diagnosis, created by using the results of at least two component tests (9). HRCT and history of exposure were selected as component tests on the basis of clinical practice and because they are independent tests given the disease status, as the HRCT assessor was blinded to clinical data. As shown in e-Table 1, because there is no agreement on how to combine the two tests, we

used two pre-defined rules to reclassify all patients in our cohort as having or not having HP (HP+ and HP-, respectively). The first rule, called AND-CRS, defined as HP+ only patients positive for both component tests. The second rule, called OR-CRS, classified as HP+ patients with either test positive (10). The AND-CRS may classify some patients having HP as not having it, and this will cause an unduly decrease in the specificity of precipitins: some patients will be positive to precipitins, have HP but considered false positive by the AND-CRS. Conversely sensitivity will be almost unbiased. The OR-CRS may classify some patients not having HP as having it, and this will cause an unduly decrease in the sensitivity of precipitins: some patients will be negative to precipitins, not have HP but considered false negative by the OR-CRS. Conversely, specificity will be almost unbiased. We consequently evaluated sensitivity against AND-CRS and specificity against OR-CRS (11).

Sensitivity was calculated as the number of subjects with positive precipitins test and defined as HP+ by MDD/CRS, divided by the number of subjects defined as HP+ by MDD/CRS; specificity as the number of subjects with negative precipitins test and defined HP- by MDD/CRS, divided by the number of subjects diagnosed as HP- by MDD/CRS. We also calculated positive and negative predictive values (12). Continuous variables were expressed as median and I-III quartiles (i.e. 25$^{th}$ and 75$^{th}$ percentiles). Categorical data were described by frequencies and percentages of subjects falling in each category. Analyses were performed using SAS (v. 9.3, SAS Institute Inc., Cary, NC, USA) and R (v. 3.1, R Foundation for Statistical Computing, Vienna; Austria) software.

## Results

### *General characteristics*

Between October 2008 and September 2011, 108 patients (median age 69 years, 54% males) were referred to our outpatient clinic with a presumptive diagnosis of fibrosing ILD. Demographics and clinical data are shown in Table 1.

The majority of patients experienced respiratory symptoms (96%) but no systemic symptoms (71%).

Definitive diagnosis reached after MDD, none of which ever changed during mean follow-up time

**Table 1.** Demographics, clinical and diagnostic data in the study cohort, overall and by final diagnosis

| Variable | Definitive diagnosis at MDD, N of patients (%) | | | | Total, |
|---|---|---|---|---|---|
| | Chronic HP | NSIP | IPF | Others | N of patients (%) |
| | 18 (17) | 45 (42) | 20 (18) | 25 (23) | 108 |
| Age* (years) | 60 (53-74) | 72 (63-75) | 70 (64-73) | 67 (53- 73) | 69 (60-74) |
| Gender | | | | | |
| Female | 10 (56) | 23 (51) | 8 (40) | 9 (36) | 50 (46) |
| Male | 8 (44) | 22 (49) | 12 (60) | 16 (64) | 58 (54) |
| Respiratory symptoms | 17 (94) | 44 (98) | 20 (100) | 23 (92) | 104 (96) |
| Systemic symptoms | 3 (17) | 14 (31) | 4 (20) | 10 (40) | 31 (29) |
| 1$^{st}$ HRCT diagnostic hypothesis | | | | | |
| Chronic HP | 18 (100) | 20 (44) | 9 (45) | 9 (36) | 56 (52) |
| NSIP | 0 (0) | 22 (49) | 5 (25) | 6 (24) | 33 (31) |
| IPF | 0 (0) | 0 (0) | 6 (30) | 1 (4) | 7 (6) |
| Others | 0 (0) | 3 (7) | 0 (0) | 9 (36) | 12 (11) |
| BAL | 13 (25) | 24 (46) | 7 (14) | 8 (15) | 52 (48) |
| Lymphocytes ≥30% | 4 (31) | 7 (29) | 1 (14) | 4 (50) | |
| Neutrophils ≥5% | 12 (92) | 19 (79) | 7 (100) | 4 (50) | |
| Surgical biopsy diagnosis | 2 (16) | 3 (25) | 2 (16) | 5 (42) | 12 (11) |

BAL: bronchoalveolar lavage; HP: hypersensitivity pneumonitis; HRCT: high resolution computed tomography; IPF: idiopathic pulmonary fibrosis; MDD: multidisciplinary discussion; NSIP: non-specific interstitial pneumonia

* Age is presented as median (I-III quartiles)

of 26 months, were chronic HP in 18 cases (17%), fibrosing NSIP in 45 cases (42%) [idiopathic in 24 cases; interstitial pneumonia with autoimmune features (IPAF) in 11 cases, associated with connective tissue diseases (CTDs) in 10 cases], IPF in 20 cases (18%) and others in 25 cases (23%, 6 sarcoidosis, 5 amiodarone-induced pulmonary fibrosis, 4 bronchiolitis obliterans organizing pneumonia, 4 combined pulmonary fibrosis and emphysema syndrome with NSIP pattern, 3 bronchiectasis and bronchiolitis, 2 drug-induced interstitial pneumonia, 1 Langerhans cell histiocytosis).

Table 1 also report overall results of diagnostic tests. Interestingly, when chronic HP was the first HRCT diagnostic hypothesis (56 cases, 52%), MDD reduced the number of chronic HP diagnosis to 18 cases. Bronchoscopy and BAL were performed only in 52 patients (48% of the whole cohort, Table 1). This sub-group showed an higher prevalence of chronic HP compared to patients not undergoing BAL (25% vs 17%). Lymphocytosis was found only in 31% of patients undergoing BAL and having a definite MDD diagnosis of chronic HP. Surgical lung biopsy was performed in 12 patients and led to diagnosis of: chronic HP in 2 cases (16% of biopsied patients), NSIP in 3 cases (25%), IPF in 2 cases (16%) and others in 5 cases (42%).

*Diagnostic role of precipitins*

Using MDD as the reference standard, serum precipitating antibodies were positive in 13 of 18 patients with a diagnosis of chronic HP, resulting in a sensitivity of 72%, and negative in 61 over 90 patients with a different diagnosis, resulting in a specificity of 68% (Table 2).

Using the composite reference standards, sensitivity against the AND-CRS was 55%; specificity against the OR-CRS was 61% (Table 2). On the basis of these results, we can expect true sensitivity of precipitins lying somewhere between 55 and 72%, and specificity between 61 and 68%. Table 2 reports also predictive values of precipitins using the different reference standards.

Retrospectively examining our cohort, if chronic HP was not the first HRCT diagnostic hypothesis with a confidence ≥ 60%, no further test was deemed necessary at MDD. In fact no patient with a negative HRCT (n=52 patients, 48%) has been reclassified as having chronic HP during the multidisciplinary evaluation. Whereas, if the first HRCT diagnostic hypothesis was chronic HP (n=56 patients, 52%), we found that the higher was the confidence of the radiologist, the lower is the percentage of false positives (Table 3).

**Table 2.** Diagnostic accuracy of precipitins against three different reference standards: multidisciplinary diagnosis (MDD), and AND and OR composite reference standards (CRS)

| Reference standard | | | Precipitins diagnostic accuracy | | | |
|---|---|---|---|---|---|---|
| | Chronic HP + | Chronic HP- | Sn | Sp | PPV | NPV |
| MDD | 18 | 90 | **72.2** | **67.8** | 31.0 | 92.4 |
| AND-CRS | 22 | 86 | **54.5** | 65.1 | 28.6 | 84.8 |
| OR-CRS | 72 | 36 | 38.8 | **61.1** | 66.7 | 33.3 |

Sn: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value
HP: Hypersensitivity Pneumonitis

**Table 3.** Distribution of final consensus diagnosis (MDD) of chronic hypersensitivity pneumonitis (HP) vs. others interstitial lung diseases (non-HP) in the 56 cases where HP was the first diagnostic hypothesis at high resolution computed tomography (HRCT), according to the level of confidence of the radiologist and corresponding classification error

| MDD diagnosis | Confidence of chronic HP diagnosis at HRCT, N of patients | | | | | Total, |
|---|---|---|---|---|---|---|
| | 60% | 70% | 80% | 90% | 100% | N |
| HP | 0 | 4 | 3 | 4 | 7 | 18 |
| non-HP | 6 | 16 | 5 | 3 | 8 | 38 |
| False positive % (95% CI) | 100% | 80% (55-92) | 62% (23-86) | 43% (10-73) | 53% (26-74) | 56 |

Based on this finding, in Figure 1 we described how precipitin test changed the final diagnosis if the first diagnosis at HRCT was chronic HP.

HRCT first diagnostic hypothesis of chronic HP associated with exposure history lead to a MDD diagnosis of chronic HP in 16 patients (89% of all patients diagnosed with chronic HP) regardless of precipitins. Positive serum precipitins led to the diagnosis of two additional patients despite a negative referred history of exposure (11%).

## Discussion

Our retrospective analysis determined that the true sensitivity of serum precipitating antibodies ranged between 55% and 72%, while the specificity between 61% and 68%, indicating a low diagnostic accuracy (11), also when considering the upper bounds. Of note, these bounds are expected to be overestimated because of incorporation bias when using MDD as the reference standard (8).

In the HP Study Group investigation (5), precipitating antibodies were found in 78% of patients with a final diagnosis of HP and only in 31% of controls. In our cohort, serum precipitins were detected in 72% of patients with a definitive MDD diagnosis of chronic HP, compared with 32% of patients classified as HP- by consensus.

This finding is consistent with the known high rate of false positive and false negative in precipitins tests. In our sample, even when MDD was the reference standard, with the associate incorporation bias described before, precipitins were not detected in 28% of patients affected by chronic HP. Precipitating antibodies may be detected in the serum of indi-

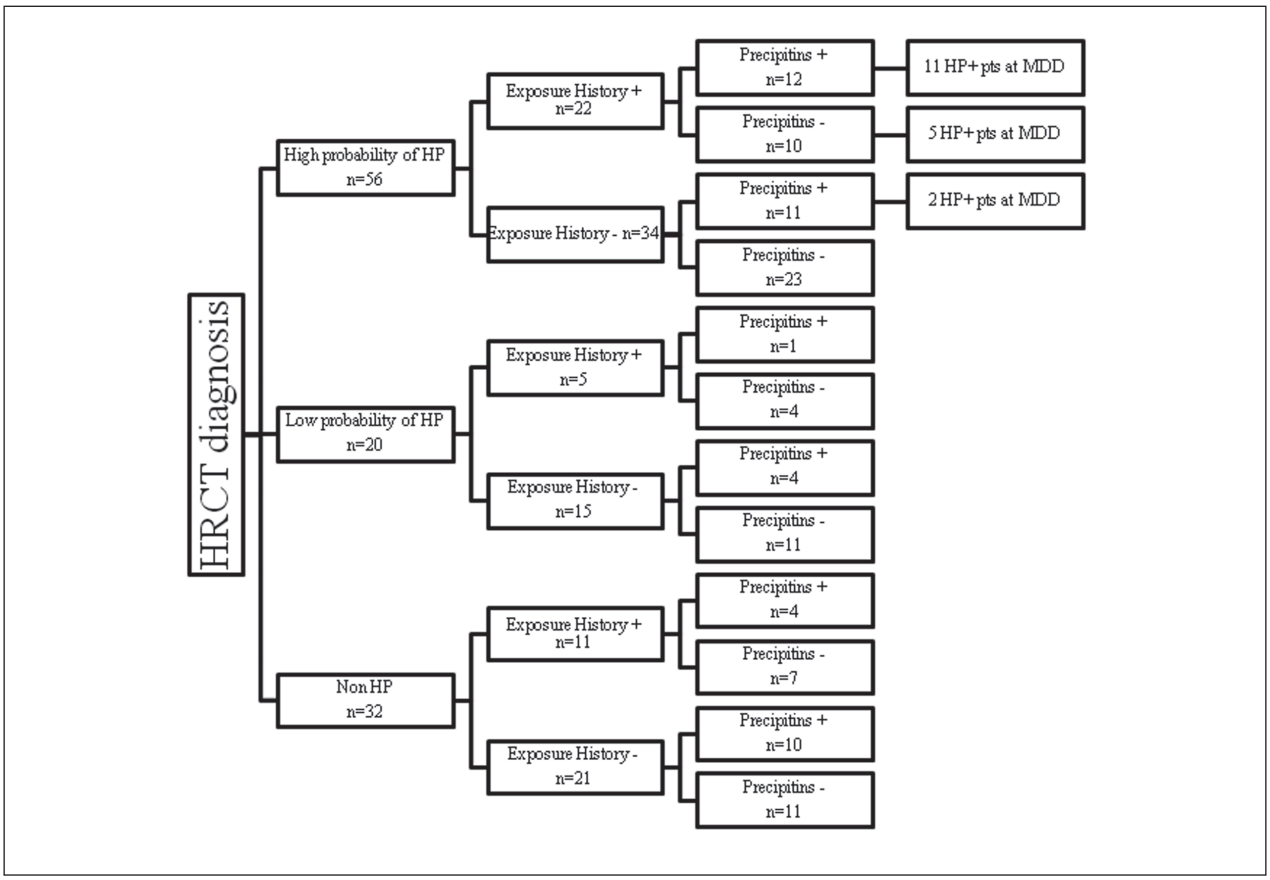


**Fig. 1.** The diagram shows the diagnostic management of the 108 patients affected by non pre-selected ILD, moving from high resolution computed tomography (HRCT) diagnostic hypothesis to precipitins test, and leading to a definitive diagnosis of chronic hypersensitivity pneumonitis (HP) in 18 cases at multidisciplinary discussion (MDD)

viduals exposed to specific antigens without signs or symptoms of HP (13). For example, precipitins were reported in up to 30% of farmers and up to 50% of pigeon breeders in absence of clinical disease (14,15). Falsely negative results may be due to antigens not included in the used commercial assay, to the disappearance of serum antibodies approximately after 2-3 years from the cessation of exposure (16), and to gradual decrease in serum titer after repeated exposure to high levels of antigen (17,18). Finally, the test may be non-reactive in some cases, even if the correct antigen is included, because of the use of poorly purified antigens, the failure to properly concentrate the patient's serum and the decreased precipitins concentration due to smoking (19).

Although some authors considered precipitins a good indicators of exposure (20-23), we found that 60% of subjects with positive precipitins referred no exposure, whereas the 32% of subjects with negative precipitins referred a known exposure. Similarly, Fenoglio et al. (24) observed that 20% of subjects with positive precipitins had no identified exposure, whereas 25% of subjects with negative precipitins had a recognized exposure.

Domestic, occupational or recreational exposure to a known offending antigen seems to have the best accuracy in chronic HP diagnosis. This result nicely fits with the finding of the HP Study Group demonstrating that exposure (present in 97% of the study subjects with HP) was the strongest single predictor of HP with an odds ratio of 38.8 (5).

In our cohort, a diagnosis of chronic HP was reached through MDD in two cases with no history of exposure (11.1% of chronic HP patients), whereas such eventuality occurred only in 1.5% of the HP Study Group's cohort (5). Even the anamnestic research of exposure may suffer from falsely negative results: the clinician may investigate only superficially the working and recreational habits of the patients or may lack expertise in occupational medicine to research hidden exposure in working environment. Moreover, the individual may be exposed to an unknown inciting antigens, especially in the domestic setting. Morrel et al. demonstrated that the majority of IPF cases originally diagnosed on the basis of 2011 criteria and subsequently diagnosed with chronic HP were attributed to exposure of occult avian antigens from commonly used feather bedding (the so-called feather duvet lung) (25).

Analysing how precipitating antibodies change final diagnosis depending on the fact that chronic HP was or was not the first HRCT diagnostic hypothesis, we found that if chronic HP was not the first diagnostic hypothesis (with a confidence ≥ 60%) no patients had been reclassified as having chronic HP during the multidisciplinary evaluation. However, in published studies evaluating biopsy confirmed chronic HP, HRCT does not have a 100% sensitivity (26). Furthermore, there is usually moderate to high inter-reader agreement in the literature for the diagnosis of chronic HP(27). We analyzed HRCT-based classification in relationship with the confidence expressed by the radiologist, and, despite the presence of the incorporation bias, a clear trend of decreasing error with increasing confidence was shown.

In terms of evaluating diagnostic accuracy, the main limitation of our single-centre retrospective study is that surgical lung biopsy was performed only in 11% of the cohort. However, the problem of missing gold standard is inherent to the disease course, as many patients evaluated for ILD cannot undergo surgical biopsy because of age, comorbidities or an already compromised lung function. Moreover, the pathological pattern of usual interstitial pneumonia is not pathognomonic of IPF because it has been described also in chronic HP, collagen vascular diseases and asbestosis. Furthermore, none of the definitive diagnosis reached after MDD ever changed during 26 months of mean follow-up time. Another potential limitation addressed in our analysis is that MDD adopted as reference standard, included the diagnostic test under evaluation, resulting in incorporation bias (8).

In conclusion, during the diagnostic management of non pre-selected cases of fibrosing ILD, serum precipitins demonstrated to give a low additional value to HRCT and history of exposure in identifying chronic HP cases. This finding emphasizes the role of an accurate history collection during the diagnostic management of fibrosing ILD, in order to recognize even subtle but persistent or recurrent exposure to antigens. Such exposure might cause asymptomatic lung disease progressing to advanced pulmonary fibrosis that may go unrecognized as chronic HP. Future prospective multicenter studies are needed to validate our findings, and to define the best algorithm to approach the diagnosis of fibrosing ILD.

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