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Assessment of current practice in the diagnosis and therapy of idiopathic pulmonary fibrosis☆

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Summary
Background: The consensus statement on the Diagnosis and Therapy of Idiopathic Pulmonary Fibrosis (IPF) formulated by the American Thoracic Society/European Respiratory Society (ATS/ERS) was published in 2000. Acceptance and implementation of these guidelines have not been assessed. We surveyed the fellows of the American College of Chest Physicians (FCCP) to establish current practice patterns regarding the diagnosis and therapy of IPF.
Methods: We electronically distributed a 32-item questionnaire to all 6443 pulmonary medicine board-certified Fellows of the American College of Chest Physicians. The response rate was 13%. Demographic characteristics were similar between respondents and non-respondents.
Results: Seventy-two percent of respondents were familiar with the ATS/ERS consensus statement and 63% found it clinically useful. However, a similar number of respondents indicated that an update is needed. Bronchoscopy and surgical lung biopsy are used infrequently. Forty-five percent of pulmonary physicians advocate providing only supportive care for patients outside of clinical trials. If pharmacological therapy is recommended, prednisone (either alone or in combination with azathioprine) or off-label agents are preferentially prescribed. Despite physician awareness (79%) of clinical trials, interested patients are not consistently referred (54%). A majority of respondents (61%) felt that lung transplantation represents the only effective therapy for IPF, and 86% refer their patients to lung transplant centers.

Abbreviations: ACCP, American College of Chest Physicians; ANA, antinuclear antibodies; ATS, American Thoracic Society; ENA, extractable nuclear antigens; ERS, European Respiratory Society; FCCP, Fellow of the American College of Chest Physicians; HRCT, high-resolution computed tomography; ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; RF, rheumatoid factor; TTE, transthoracic echocardiography; UIP, usual interstitial pneumonia.

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Conclusions: There is substantial variability among pulmonary physicians in the diagnosis and management of IPF. This may, in part, reflect the current lack of effective pharmacologic therapy. Updated practice guidelines are needed for the diagnosis and therapy of IPF.

Background

Idiopathic pulmonary fibrosis (IPF) is a devastating, progressive lung disease as illustrated by a median survival from diagnosis of approximately 3 years.[1] Over the past decade there have been several conceptual changes in the diagnostic and therapeutic approach to patients with IPF.[2–4] In the year 2000, the American Thoracic Society (ATS) and European Respiratory Society (ERS) published a joint international consensus statement incorporating these new developments.[1] This document defined IPF as a progressive chronic interstitial lung disease of unknown cause associated with a histopathologic pattern of usual interstitial pneumonia (UIP).[1] Patients with compatible clinical and radiologic features combined with a histopathologic confirmation of UIP on surgical lung biopsy have ''definite'' IPF.[1] A diagnosis of ''probable'' IPF is assigned if several clinical and radiologic criteria are met in the absence of a surgical lung biopsy.[1] Several high-resolution computer tomographic (HRCT) findings have been delineated that correlate with the histopathologic pattern of UIP.[5–8]

While new diagnostic criteria have been developed, treatment of IPF remains difficult.[1] In the absence of effective therapy, the ATS/ERS document suggests combination therapy with prednisone and azathioprine or cyclophosphamide as an option for initial treatment.[1] In recent years, several studies have suggested possible therapeutic effects from non-immunosuppressive agents such as *N*-acetylcysteine and anticoagulation in patients with IPF.[9,10] In addition, several new pharmacologic agents (e.g. interferon-gamma, pirfenidone, etanercept, imatinib, and bosentan) have been investigated in clinical trials.[11,12]

The goal of this survey was to assess current practice patterns and attitudes of pulmonologists in the diagnosis and management of patients with IPF. Furthermore, we hoped to identify current dilemmas and additional issues that may need to be addressed in forthcoming practice guidelines.

Methods

We designed a 32-item questionnaire to characterize current clinical practice patterns regarding the evaluation and treatment of IPF patients by pulmonologists (see online supplement for questionnaire).

This questionnaire was developed to specifically collect data regarding:

1. Familiarity with and utilization of the ATS/ERS consensus statement on IPF[1] (2 questions).
2. Current diagnostic strategies employed for patients with suspected IPF (11 questions).
3. Therapeutic interventions recommended for patients diagnosed as having IPF (11 questions).

In addition, we gathered demographics of the respondents and data regarding the frequency with which they encountered IPF patients (8 questions).

We used the software SurveyTracker (TrainingTechnologies, Lebanon, OH) to convert the questionnaire into an online survey. The online survey was piloted within the Division of Pulmonary and Critical Care Medicine at the Mayo Clinic, Rochester, MN. Based on the comments received, we modified the survey. The American College of Chest Physicians (ACCP) approved this online survey as an ACCP-Interstitial Lung Diseases (ILD) Network project. The Mayo Clinic Institutional Review Board also approved this project.

On December 15, 2006, an e-mail announcing the upcoming IPF survey was sent to all Fellows of the American College of Chest Physicians (FCCP) who are board-certified in Pulmonary Medicine ($n = 6443$). This announcement was followed on December 18, 2006 by another e-mail providing the recipients with a link to the online survey. A reminder was sent to all potential participants on January 3, 2007 and the survey closed on January 17, 2007. All responses were electronically collected, summarized and analyzed using the SurveyTracker (TrainingTechnologies, Lebanon, OH) software. All data were de-identified.

The Chi-Square test (χ^2) (GraphPad Software, San Diego, CA) was used to compare the demographics of the respondents and all potential participants, and to perform the subgroup analysis by the year of fellowship completion and practice setting. Respondents practicing in both private and academic settings responded similarly to pulmonary physicians in private practice and were therefore combined for subgroup analysis.

Results

Eight hundred and fourteen individuals (13%) of the invited physicians completed the survey; 36 individuals stated that they do not encounter patients with interstitial lung diseases (ILD) and were excluded. The median response rate of all respondents to the individual questions was 99.6% (range, 77.1–100%).

Table 1 compares the demographics for the 778 respondents and the entire cohort of the invited participants. There were no significant differences between the invited participants and the respondents in regard to gender, year of fellowship completion, and practice location. Compared to the invited cohort, the survey respondents tended to be slightly younger ($p = 0.32$).

Since the ACCP membership database does not include any information about the practice setting we were unable to compare the respondents to the entire cohort in this regard.

The survey respondents have a substantial ILD/IPF practice. Sixty-six percent of respondents saw at least 2 ILD patients per week and 38% of the respondents evaluated at least 2 IPF patients per week (Fig. 1).

Table 1 Comparison of demographic information between the invited participants and the survey respondents

	Invited participants ($n = 6443$)	Respondents ($n = 778$)	p-Value (χ^2)
Age group (%)			
Less than 40 years	9	14	0.32
41–50 years	38	38	
51–60 years	35	38	
Over 60 years	18	10	
Gender (%)			
Men	88	87	0.83
Women	12	13	
Year of completion of fellowship (%)			
Before 1990	50	51	0.92
1990–2000	35	36	
After 2000	15	13	
Practice location (%)			
US	85	82	0.70
Outside US	15	18	
Practice setting (%)			
Private	NA	51	NA
Academic	NA	31	
Both	NA	14	
Other	NA	4	

Utilization of the current ATS/ERS IPF consensus statement

Seventy-two percent [95% CI 69–75%] of all respondents were familiar with the ATS/ERS consensus statement and 63% [95% CI 59–67%] of them considered it clinically useful. The majority of participants (63% [95% CI 58–66%]) felt that an update of this consensus statement is needed. These responses did not vary based on practice setting or time since completion of fellowship training. Sixty-four percent [95% CI 60–68%] of all participants stated that they use the diagnostic criteria for ''definite'' and ''probable'' IPF as outlined in the consensus statement. Physicians who graduated from fellowship training after the year 2000 or practice pulmonary medicine in an academic setting used these criteria more commonly, graduates >2000 (75% [95% CI 65–83%]) versus ≤2000 (62% [95% CI 58–66%]), $p = 0.02$ and physicians in academic practice (76% [95% CI 70–82%]) versus private/academic practice (58% [95% CI 53–63%]), $p > 0.001$.

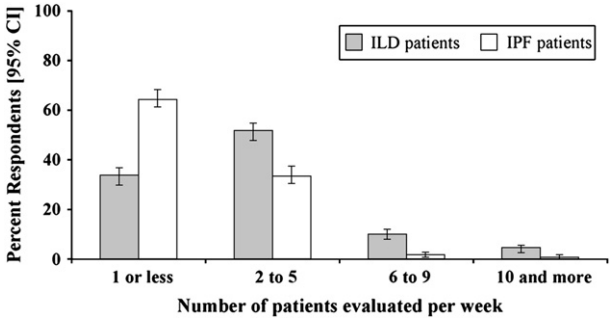

Figure 1 Frequency of interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF) patients encountered by the survey respondents.

Diagnosis of IPF

Seventy-three percent [95% CI 69–76%] of the respondents obtain HRCT for every patient with suspected IPF; academic pulmonologists reported the higher universal utilization of HRCT (academic practice 80% [95% CI 74–85%] versus 73% [95% CI 66–74%] private/academic practice, $p = 0.003$). Most pulmonologists indicated that they order antinuclear antibodies (ANA) (98%, 95% CI 96–99%) and rheumatoid factor (RF) (94%, 95% CI 92–95%) [Fig. 2]. Subgroup analysis revealed significant differences regarding the use of other serologic markers. Academic pulmonologists more commonly order anti-double-stranded DNA antibodies (43% [95% CI 37–50%] versus 31% [95% CI 27–36%], $p = 0.002$), antibodies against extractable nuclear antigens (ENA) (60% [95% CI 54–66%] versus 45% [95% CI 38–47%], $p < 0.001$) and creatine kinase (42% [95% CI 35–48%] versus 27% [95% CI 22–29%], $p < 0.001$) compared to private/academic pulmonologists. Physicians, who graduated before 1990, less frequently order anti-ds-DNA antibodies (30% [95% CI 26–35%] versus 42% [95% CI 35–45%], $p = 0.004$) and anti-ENA-antibodies (42% [95% CI 37–47%] versus 56% [95% CI 48–58%], $p = 0.003$) but more commonly order a hypersensitivity serologic panel (47% [95% CI 42–52%] versus 37% [95% CI 33–43%], $p = 0.007$).

The majority of pulmonary physicians (57% [95% CI 53–60%]) responding to our survey utilize surgical lung biopsy in ≤30% of patients with suspected IPF. Similarly, the majority of respondents (62% [95% CI 58–65%]) perform bronchoscopy in <50% of their suspected IPF cases; pulmonologists in private/academic practice employ bronchoscopy less frequently compared to those in academic settings (68% [95% CI 62–70%] versus 54% [95% CI 48–60%], $p = 0.002$). The tests performed during bronchoscopy are outlined in Fig. 3.

If a surgical lung biopsy is performed, most physicians (78% [95% CI 75–80%]) use HRCT to determine the biopsy site; recent graduates (after the year 2000) of pulmonary fellowship programs utilize HRCT more frequently (86% [95% CI 78–92%] versus 77% [95% CI 73–80%], $p = 0.003$) for this purpose. Eighty percent [95% CI 77–83%] of respondents request the surgeon to biopsy more than one lobe.

Recent evidence suggests that both the 6-min walk test and transthoracic echocardiogram (TTE) can be used to risk stratify patients with IPF. The majority of respondents report using the 6-min walk test to assess exercise capacity and disease progression (66% [95% CI 62–69%]), and order TTE to evaluate patients with suspected IPF for pulmonary hypertension (76% [95% CI 73–79%]).

Therapeutic interventions in patients with IPF

The majority of respondents (61% [95% CI 57–64%]) felt there is currently no effective pharmacologic therapy for

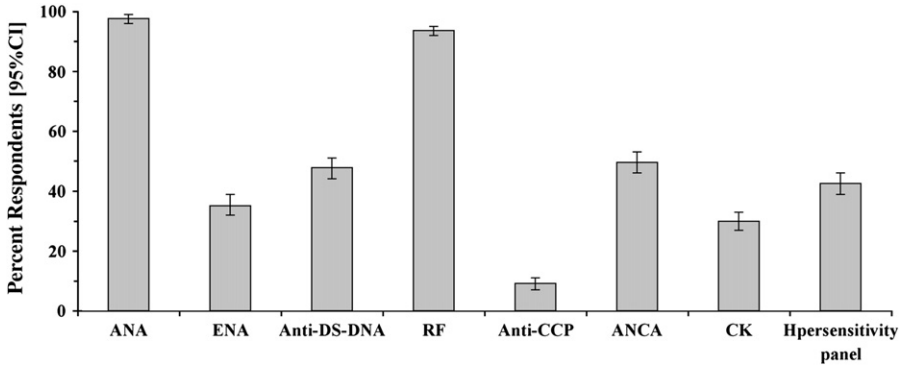

Figure 2 Utilization of serologic markers in the diagnostic workup of patients with idiopathic pulmonary fibrosis. ANA, antinuclear antibodies; ENA, anti-extractable nuclear antigens antibodies; Anti-DS-DNA, anti-double stranded DNA antibodies; RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; CK, creatine kinase.

IPF other than lung transplantation. However, 55% [95% CI 52—59%] of the respondents stated they use pharmacological therapy for IPF patients who are not candidates for lung transplantation. Eighty-six percent [95% CI 83—88%] of the respondents stated they refer their IPF patients to a lung transplant center for evaluation.

The survey questionnaire included two case scenarios (see online supplement) for which the respondents were asked to select a preferred treatment regimen. The first case illustrated a patient with histologically confirmed UIP and radiologic features of mild IPF characterized by prominence of ground-glass opacities and minimal fibrosis. In contrast, the second case described a patient with advanced IPF including radiologic features of advanced honeycombing and only minimal associated ground-glass opacities, but without a surgical lung biopsy confirmation.

There was a broad range of responses indicating heterogeneity of treatment preferences. For the first case (mild IPF), most common choices included prednisone alone (30% [95% CI 25—34%]), combination of prednisone, azathioprine and *N*-acetylcysteine (27% [95% CI 23—31%]), and prednisone combined with azathioprine (18% [95% CI 14—21%]) or cyclophosphamide (8% [95% CI 6—11%]). For the second case (advanced IPF), fewer participants chose prednisone alone (20% [95% CI 17—24%]) but the proportions favoring the combination of prednisone, azathioprine and *N*-acetylcysteine (27% [95% CI 23—32%]), and prednisone combined with azathioprine (16% [95% CI 13—20%]) or cyclophosphamide (5% [95% CI 3—8%]) were comparable to Case 1. Overall, approximately one-half of physicians recommended therapies in accordance with the ATS/ERS IPF consensus statement (52.5% in Case 1 and 48.5% in Case 2). Interestingly, non-immunosuppressive therapies such as monotherapy with *N*-acetylcysteine (12% [95% CI 10—16%] Case 2 versus 8% [95% CI 6—11%] Case 1), systemic anticoagulation (4% [95% CI 3—7%] Case 2 versus 1% [95% CI 0.4—3%] Case 1) or off-label use of novel therapeutic agents (11% [95% CI 9—15%] Case 2 versus 8% [95% CI 5—10%] Case 1) was more commonly suggested for the case of advanced IPF (Case 2) (Fig. 4).

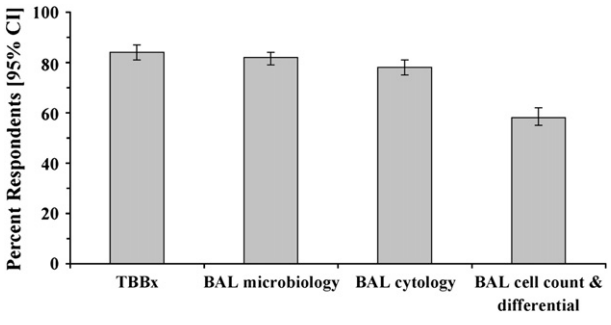

Figure 3 Bronchoscopic procedures in the diagnostic evaluation of patients with idiopathic pulmonary fibrosis. BAL, bronchoalveolar lavage; TBBx, transbronchial biopsy.

For Case 1, treatment choice varied based on the practice setting of the respondents (academic versus private practice, $p = 0.046$). Pulmonologists in academic practice were less likely to use prednisone alone or off-label therapies but more commonly prescribed prednisone in combination with azathioprine and *N*-acetylcysteine as well as *N*-acetylcysteine alone compared to their colleagues in private practice. No such differences were observed for Case 2.

In general, prednisone either alone or in combination with other immunosuppressive agents was more commonly recommended in the first case (82% [95% CI 78—85%]) compared to the second case (69% [95% CI 64—73%]).

The majority of clinicians (79% [95% CI 76—81%]) are aware of clinical trials in their geographic region. However, 46% [95% CI 42—50%] of respondents indicated that they do not or only sometimes refer patients to these centers. Pulmonologists in academic/private practice and those who completed their fellowship training prior to 1990 reported less consistent (''always'') referrals to clinical trials (17% [95% CI 14—21%] private versus 21% [95% CI 21—33%] academic, $p = 0.004$ and fellowship <1990, 14% [95% CI 11—19%] versus >1990 26% [95% CI 22—32%], $p = 0.003$).

Twenty-five percent [95% CI 22—28%] of respondents reported treating all IPF patients, regardless of symptoms for GERD. Forty-four percent [95% CI 40—48%] of the remaining respondents reported screening all asymptomatic patients with IPF for gastroesophageal reflux disease (GERD). The most commonly employed therapy was the

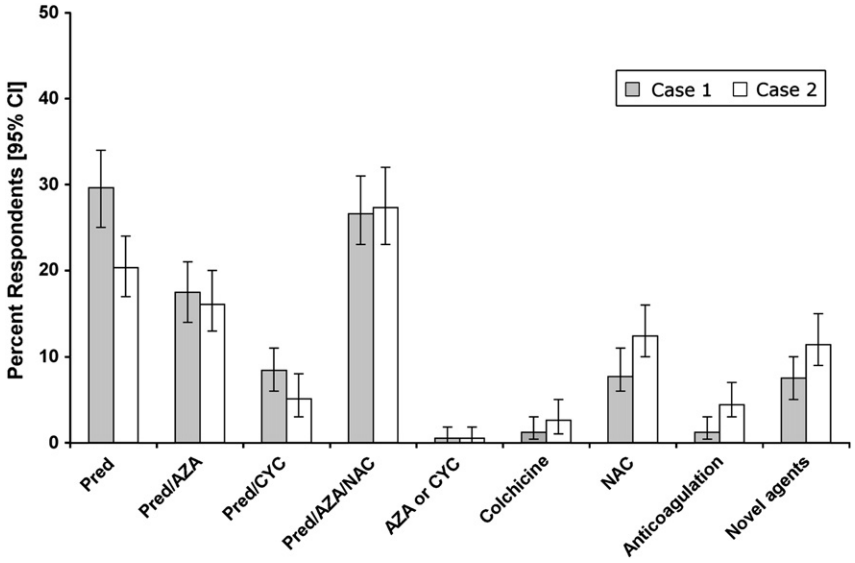

Figure 4 Utilization of various pharmacologic therapies for patients with idiopathic pulmonary fibrosis. (A) Case 1, patient with histologically confirmed UIP and radiologic features of mild IPF characterized by prominence of ground-glass opacities and minimal fibrosis. (B) Case 2, patient with advanced IPF including radiologic features of advanced honeycombing and only minimal associated ground-glass opacities, but without a surgical lung biopsy confirmation.

combination of lifestyle modifications and a proton pump inhibitor (PPI).

Eighty-three percent [95% CI 80—85%] of respondents indicated that pulmonary hypertension detected by TTE alters their treatment approach. Most respondents (82% [95% CI 79—84%]) considered pulmonary hypertension to be an indicator of poor prognosis. Forty-two percent [95% CI 38—45%] of respondents contemplate vasomodulator therapy and 33% [95% CI 30—37%] think about the initiation of anticoagulant therapy for pulmonary hypertension.

The frequencies of other supportive measures are outlined in Fig. 5. Both, referral to pulmonary rehabilitation and the discussion of end of life issues were less likely if the physicians had completed their fellowship training prior to 1990 (76% [95% CI 71—80%] versus 87% [95% CI 83—90%], $p < 0.001$ and 80% [95% CI 75—83%] versus 86% [95% CI 83—90%], $p = 0.01$).

Discussion

We believe our survey to represent the largest and most inclusive synopsis of the current approach to the diagnosis and treatment of IPF. We were able to capture a representative sample of pulmonologists in both academic and private practice who encounter a large number of IPF patients indicative of a high level of clinical experience. Our survey is the first attempt to formally assess the level of familiarity and acceptance of the ATS/ERS consensus statement. Seventy-two percent of our survey respondents reported that they were familiar with the ATS/ERS consensus statement. This level of familiarity compares quite favorably to other similar guidelines. A systematic review by Cabana et al. reported a median level of familiarity of 43.5% with a range between 11% (American College of Physicians exercise stress testing guidelines) and 100% (Asthma guideline).[13] Nevertheless, considering the controversies surrounding the management of IPF patients, the lack of familiarity with this document by 28% of the survey participants 7 years after its publication is troublesome and may hinder its implementation.[13]

The majority of the pulmonologists familiar with the ATS/ERS statement (64%) use the diagnostic criteria provided by the consensus statement. Although these criteria necessitate the performance of either a surgical lung biopsy or flexible bronchoscopy with transbronchial biopsy and/or bronchoalveolar lavage, most patients with IPF do not appear to undergo either surgical lung biopsy or bronchoscopy. The infrequent utilization of these procedures during the diagnostic workup of patients with suspected IPF is consistent with data previously reported by other authors and may be attributable to recent advances in HRCT diagnosis of IPF.[5—8,14,15] A recent survey demonstrated that 67.4% of the participating pulmonologists would accept an HRCT diagnosis of IPF in the absence of a confirmatory

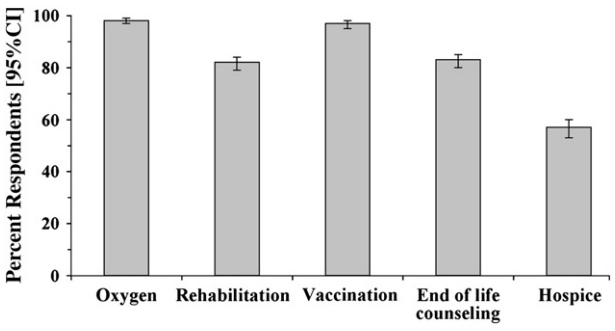

Figure 5 Utilization of supportive measures in the care of patients with idiopathic pulmonary fibrosis.

tissue biopsy.[8] Our survey did not assess the reasoning behind the respondent's decision to not perform a surgical lung biopsy.

In the absence of effective pharmacologic therapy, the management of IPF patients remains contentious. Sixty-one percent of all pulmonary specialists completing our survey believe that besides lung transplantation there are no effective therapeutic options. Nearly one-half of the respondents in our survey manage their IPF patients with supportive care alone, a trend that has been also documented by others.[14,15] For example, 77% of British pulmonary specialists opted to observe when presented with an elderly patient with IPF and minimal symptoms.[14] In contrast, Collard et al. reported a conservative treatment approach by only 9% of academic pulmonary specialists in the US.[16]

There was no consensus regarding choice of pharmacologic agents among pulmonologists favoring pharmacotherapy for IPF. Prednisone continues to be the most commonly used agent, which is similar to the observations made in other recently published studies.[14,15]

Overall there is a relatively low level of acceptance of the recommendations for the diagnosis and management of IPF provided by the ATS/ERS consensus statement. Aside from lack of familiarity with the document, several other factors may influence guideline adherence.[13] Over the past several years the role of HRCT and bronchoscopy in the diagnosis of IPF has been clarified, necessitating revisions of the original guideline published in 2000. There has also been increasing doubt regarding the potential effectiveness of corticosteroids and immunosuppressive agents in the management of IPF. Accordingly, the majority of respondents felt that the ATS/ERS guidelines need to be updated.[13]

Despite the prevalent awareness of clinical trials for the treatment of IPF, our survey showed that treating pulmonologists frequently choose not to refer interested patients for these studies. One potential reason for this phenomenon may be the fear of adverse outcomes related to aggressive diagnostic evaluation, e.g., surgical lung biopsy or study drugs.[17] Alternatively, these decisions could be influenced by geographic limitations, concerns of the physicians regarding placebo-controlled study design or preconceived notions about the effectiveness of the study drug.

Seven years following the publication of the ATS/ERS consensus statement, there are now several surveys assessing the current strategies employed for diagnosis and management of IPF. Collard et al. conducted an electronic survey of academic pulmonologists in the United States.[16] However, this survey had several limitations. The authors intended to survey all pulmonologists practicing in academic centers with an accredited training program. Out of 130 such centers, they only obtained contact information for practitioners from 42 centers (32%).[16] Because three of the responding programs did not provide individual contact information but distributed group e-mails, the actual number of invited individuals remains elusive. The estimated sample included only approximately 10% of the target group.[16] Furthermore, the survey design prohibited any comparison between responders and non-responders and therefore prevented an assessment whether or not this sample was representative.[16] Nevertheless, compared to our results, Collard et al. observed very similar trends regarding the use of HRCT, bronchoscopy, surgical lung biopsy and the evaluation of IPF patients for GERD and the lack of consensus regarding pharmacological therapies in their study population.[16] In contrast to our survey the physicians surveyed by Collard et al. did encounter much fewer IPF patients than the pulmonologists participating in our survey.[16] This greater level of expertise may explain why we documented more frequent referrals to lung transplantation and higher rates of treatment strategies focusing on observation and supportive care.[16] In addition, our survey addressed the issue of IPF-associated pulmonary hypertension which was not addressed in the previous study by Collard et al.

Several other recent publications also lent support to the diagnostic and management strategies for IPF patients observed in our survey. A recent case-based survey was distributed to 689 consultant members of the British Thoracic Society (370 responses [54%]). In this exercise two of three case scenarios represented patients suffering from IPF.[14] In addition, Collard et al. recently published a larger survey involving IPF patients and their caregivers (>2000 members of the Coalition for Pulmonary Fibrosis, response rate $\approx$ 50% ($n = 1448$)).[15]

There are several limitations to our study. Our survey had a relatively low response rate, which could have been due to several factors. In recent months multiple online surveys have been sent to members of the pulmonary and critical care physician community by professional subspecialty organizations. Since many of these organizations target the same individuals included in our survey, it is possible that the participants felt overloaded with these requests. This explanation is supported by the fact that recent electronic surveys conducted by the ACCP have been similarly troubled by low response rates (personal communication with ACCP). Moreover, given the current trends for pulmonary specialists to sub-specialize within the field of pulmonary medicine, it is possible that individuals who do not encounter IPF patients on a regular basis elected not to respond. Physicians responding to our survey encounter very large numbers of ILD and IPF patients, indicating that we were able to survey a group of pulmonogists caring for the majority of patients with IPF. Lastly, the fact that the initial survey invitation was sent out close to the Christmas holidays may be another contributing factor. Nevertheless, based on the absence of any significant difference in demographic variables between the respondents and the invited individuals we feel that we captured a representative population. Finally, our data only represent a snapshot in time, are based on information reported by physicians rather than objective data and therefore subject to recall bias, and our survey population was restricted to members of the ACCP who have FCCP status.

In conclusion, the results of the survey provide a synopsis of current practice patterns in the diagnosis and management of IPF. We identified several dilemmas regarding the diagnosis and management of IPF. These issues include inadequate familiarity with the practice guidelines, absence of consensus regarding pharmacotherapy of IPF, and a low level of referral to clinical trials.

Evolving knowledge regarding the use of HRCT and bronchoscopy has modified the diagnostic approach to IPF, and practice guidelines that deal with IPF diagnosis

and management need to be updated in this regard. In the absence of effective pharmacologic therapy, the management of patients with IPF remains difficult as reflected in this survey. Updated guidelines will need to include a systematic review of currently available pharmacologic agents in the management of IPF and an encouragement for clinicians to refer patients with IPF for clinical trials.

Competing interests

None of the authors has any competing interests.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2008.03.018.

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