



Published in final edited form as:

Respir Med. 2007 September ; 101(9): 2011–2016.

Current Diagnosis and Management of Idiopathic Pulmonary Fibrosis: A Survey of Academic Physicians

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SUMMARY

Little is known about practice patterns regarding the diagnosis and management of idiopathic pulmonary fibrosis (IPF). This study attempts to define the practice patterns of academic pulmonologists caring for patients with idiopathic pulmonary fibrosis. Academic pulmonologists in the United States were surveyed electronically. Completed surveys were received from 272 respondents (representing approximately 10% of academic pulmonologists). The majority agreed that high-resolution computed tomography scanning can establish the diagnosis of idiopathic pulmonary fibrosis, and that surgical lung biopsy is indicated when the diagnosis remains unclear. Bronchoscopy is little utilized. Most respondents treat patients with medications, but there is no consensus regarding treatment regimen. These results suggest there is general consensus regarding the approach to diagnosis, but that there is no consensus about medical management in IPF.

INTRODUCTION

Idiopathic pulmonary fibrosis is the most common form of idiopathic interstitial pneumonia, with an estimated prevalence of up to 42 per 100,000 people. [1] There are no proven therapies for IPF and median survival is around 3 years from the time of diagnosis. [2-5] Because of its rarity, severity and lack of response to therapy, IPF is confusing and frustrating to practicing pulmonologists.

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Conflict of Interest Statement

None of the authors has a conflict of interest to declare in relation to this work.

The American Thoracic Society (ATS), European Respiratory Society (ERS) and the American College of Chest Physicians (ACCP) produced a joint statement in 2000 outlining the current definition of IPF and recommending an approach to its diagnosis and management. [2] This statement defined IPF as a specific form of chronic fibrosing interstitial pneumonia with the histologic appearance of usual interstitial pneumonia (UIP) on surgical (thoroscopic or open) biopsy. In the absence of surgical lung biopsy, criteria for a presumptive clinical diagnosis of IPF were developed that centered around a typical appearance on high-resolution computed tomography (HRCT) scan of the chest. [2] These clinical criteria have since been validated, and although they have poor sensitivity, they are highly specific. [6-8] While careful to state that no therapy has been proven beneficial in the treatment of IPF, the ATS/ERS/ACCP statement recommended considering combination therapy with corticosteroid and cytotoxic (azathioprine or cyclophosphamide) drugs.

Little is known about current practice patterns regarding the diagnosis and management of IPF. In addition, it is unknown whether these practice patterns are consistent with the recent consensus recommendations. Academic physicians are leaders in the continuing education of the pulmonary community through publication of research and review articles, presentations at conferences, and day-to-day interaction with community providers and physicians in training. Knowledge of academic physicians' approach to caring for patients with IPF would, therefore, directly inform the current standard of care for diagnosis and management of this condition. This study was designed to define the practice patterns of academic pulmonologists caring for patients with IPF and assess the degree to which these patterns are consistent with consensus recommendations.

METHODS

Survey Population

A search for Accreditation Council for Graduate Medical Education-accredited training programs in Pulmonary and Critical Care Medicine in the United States was performed through the website (www.acgme.org/acWebsite/home/home.asp). Each program was contacted to obtain email addresses of their pulmonary and critical care faculty for use in administering an anonymous, voluntary electronic survey. Individual email addresses were requested for direct distribution of the survey. In cases where individual email addresses were not available, a central administrative contact was identified for internal distribution of the survey at that institution.

This protocol was approved by the Committee on Human Research at the University of California San Francisco and the Institutional Review Board at Vanderbilt University.

Survey Administration

The survey was electronically administered from July 1 to August 31, 2006 using a professional online survey website (www.surveymonkey.com). An introductory email describing the survey and providing a link for interested respondents was sent to all faculty or faculty administrative contacts. This was followed by two reminder emails that were sent only to those who had yet to respond. Respondents were allowed to complete a partial survey. Only one response per respondent was allowed. All responses were anonymous, they could not be linked to any respondent information not provided in the survey.

Data Analysis

Individual survey responses were compiled with additional variables (e.g. combination treatment regimens) created based on further analysis of the primary survey data. For determination of region of practice, the United States Census Bureau regions were adopted.

Summary statistics were calculated and displayed as percentages. Comparisons across demographic and geographic variables were performed using chi-squared and Fisher's exact procedures where appropriate. A p value of < 0.05 was considered statistically significant. All data analyses were performed using SAS v9.2 (SAS Institute, Cary, NC.)

RESULTS

Survey Respondents

One hundred and thirty training programs were identified. Eight hundred and thirty four individual emails were obtained from 39 programs in 22 states and the District of Columbia. Three additional institutions provided administrative email contacts and internally distributed the survey to their faculty. Assuming an equal number of faculty at each institution listed responded to the survey, this pool represents 32% of all academic pulmonologists. Responses were received from 272 respondents (33% survey response rate), or an estimated 10.5% (33% of 32%) of all academic pulmonologists in the United States. Information on individual program response rates was not available due as survey responses were anonymous. Respondents were asked to provide some general demographic information which is summarized in Table 1. There was at least one response from all 22 states and the District of Columbia. Twenty two (8%) of responses were incomplete.

Diagnosis and Monitoring

The overwhelming majority of respondents reported that a HRCT scan should be obtained in all patients suspected of having IPF (90%), and that a surgical lung biopsy should be obtained if the HRCT is atypical (76%). Seventy one percent reported that a definitive HRCT scan could establish the diagnosis of IPF in the proper clinical setting. A minority of respondents reported that a surgical biopsy should be obtained in all patients with IPF (12%). Most respondents did not feel bronchoscopy was important to the diagnosis of IPF (82%).

Most respondents (85%) reported that analysis of serial changes in both the forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) were used to judge treatment response. Other commonly reported outcome measures included breathlessness and dyspnea (74%), 6 minute walk test distance (59%), exercise oxygen saturation (55%) and HRCT appearance (50%).

Screening for Comorbidities

Thirty-five percent of respondents routinely screen for sleep apnea, generally by history and physical examination. Slightly more respondents (55%) routinely screen for gastroesophageal reflux disease, again generally by history. A minority report screening with pH probe (15%) and barium swallow (7%). The vast majority of respondents screen for exertional hypoxemia (87%), generally (59%) with formal 6 minute walk testing, and for autoimmune disease (92%), generally with history (87%), antinuclear antibody (95%), rheumatoid factor (90%) and scl-70 antibody (72%).

Acute Exacerbation of IPF

Nearly all respondents (97%) reported observing acute exacerbation of IPF, defined as acute worsening of respiratory status with no clear etiology. (Figure 1A) Nearly all respondents (87%) required a combination of subjective worsening of breathlessness and at least one objective measure to identify an episode as an acute exacerbation of IPF. Objective measures commonly required in diagnosing an acute exacerbation included: worsening oxygenation/gas exchange (92%); absence of infection (86%); absence of cardiac events (83%); and absence

of pulmonary embolism (82%). A new opacity identified on the chest CT scan was required by 49% of respondents.

Fifty-one percent of respondents reported treating acute exacerbations with corticosteroids alone; another 30% report treating with combination corticosteroids and cytotoxic therapy (azathioprine or cyclophosphamide). Eight percent of respondents reported using anticoagulation for the treatment of acute exacerbations, usually as a single agent. Most respondents reported that such events are highly morbid. (Figure 1B)

Pharmacologic Therapy

The majority of respondents reported (52%) “frequently” or “always” treating patients with IPF at the time of diagnosis. Another 35% reported treating patients with IPF “sometimes”. Twelve percent reported that they “rarely” or “never” treat IPF with medications. Most first-line treatment regimens (74%) contained prednisone with or without the addition of immunosuppressive agents and N-acetylcysteine. (Figure 2) Twenty-three percent reported using combination corticosteroid and cytotoxic therapy (azathioprine or cyclophosphamide). Salvage therapy (i.e., therapy for patients unresponsive to initial treatment) was much less likely to include prednisone (18%) and more likely to include interferon gamma 1b (17%) or no therapy (20%.) (Figure 2) Respondents seeing fewer than 5 patients with IPF a year were more likely to use prednisone alone as a first choice regimen ($p = 0.01$) and appeared less likely to report no therapy as an initial approach ($p = 0.08$) (Table 2).

Non-pharmacological Therapy

Lung transplantation was reported as a treatment option for IPF by 54% of respondents. There was significant variation in the reported use of transplantation, with higher reported use in the Midwest ($p=0.01$), in respondents in practice for less than 5 years ($p=0.01$) and in respondents seeing over 20 patients with IPF annually ($p=0.0007$.) (Table 3)

Two thirds (68%) of respondents reported that they routinely refer patients with IPF for pulmonary rehabilitation. Of those that do not refer for pulmonary rehabilitation, the majority (76%) respond that they do not do so because pulmonary rehabilitation has unproven benefit in IPF. One third (32%) of respondents reported presumptively treating patients with IPF for gastroesophageal reflux disease.

DISCUSSION

This study represents the first large-scale assessment of clinical practice patterns of academic physicians caring for patients with IPF. Importantly, this is the first survey performed since the publication of the ATS/ERS/ACCP statement on IPF [2]. The findings of this study show the following: (1) There is general consensus regarding the approach to diagnosing and monitoring IPF, and this approach is largely consistent with the consensus recommendations. The exception is the use of bronchoscopy, which is recommended but is rarely performed. (2) There is no consensus about the medical management of patients with IPF, with a minority of respondents following consensus treatment recommendations. (3) There is uniform recognition that acute exacerbations of IPF occur and that they are common and highly morbid events. (4) Lung transplantation is considered as a treatment option for half of patients with IPF.

Previous Surveys of Practice Patterns in IPF

In the last 20 years, three surveys of practice patterns in IPF have been published in the English language literature. In 1989, Smith and colleagues surveyed 109 graduates of the University of California San Diego pulmonary fellowship training program and received 25 analyzable responses (23% response rate). [9] A minority reported routine use of open biopsy (30%) while

a majority reported the use of transbronchial biopsy (65%) for the diagnosis of IPF. Initial treatment was generally with prednisone alone (72%) or prednisone plus cytotoxic agent (8%). Salvage therapy was most commonly prednisone plus cytotoxic agent (52%). Disease monitoring was by pulmonary function tests (80%), exercise studies (64%) chest x-ray (40%), gallium scan (36%) and symptoms (32%). Lung transplant was little used (4%), likely because at that time it was not widely available.

In 1993, Johnson and colleagues published a retrospective chart review of 200 IPF patients seen in the United Kingdom. [10] They found very few cases were diagnosed by surgical biopsy (8%), with a larger minority diagnosed by transbronchial biopsy (33%). Treatment was most commonly with prednisone alone (55%) and uncommonly with prednisone plus a cytotoxic agent (11%). Thirty four percent received no therapy. A follow up study by Johnson and colleagues in 1997 utilized a prospective registry of 558 patients entered by 150 providers over 2 years. [11] Their findings confirmed that surgical biopsy was rare (12%), that prednisone alone remained the most common therapy (34%), and that 48% of patients received no therapy.

Our survey expands upon these previous efforts in several important ways. First, it involves a larger sample of pulmonologists than any previous study. Secondly, it provides insight into the current standard of care being taught to practicing pulmonologists and physicians in training. Thirdly, it is broader in scope than previous surveys, investigating diagnosis, pharmacologic and non-pharmacologic management, natural history, disease monitoring and screening for comorbidities. Fourthly, it is the only study to incorporate the use of HRCT scanning. Lastly, it is the only study conducted after the ATS/ERS/ACCP statement revised the definition of IPF and recommended an approach to diagnosis and management and can therefore comment on the degree to which expert opinion is being adopted by the larger academic community.

Management Patterns in Patients with IPF

These results suggest that, unlike diagnosis, the management of IPF remains far from standardized; there is no consensus approach among academic pulmonologists. There are likely several factors involved. First, recent data on the impact of corticosteroid and cytotoxic drugs has been published that suggest a lack of efficacy and confirm the common occurrence of side effects. [12-14] Second, published studies of agents such as interferon gamma 1b, pirfenidone, and N-acetylcysteine have been interpreted as showing promise. [15-21] Third, the increasingly accepted pathophysiologic paradigm of abnormal wound healing in which inflammation plays a limited role argues against the traditional approach to therapy (corticosteroids and cytotoxic agents) proposed by the consensus statement.[22] In the absence of compelling data or rationale, pulmonologists are left to make treatment decisions based on intuition and anecdote, and this understandably leads to a variety of approaches.

Study Limitations and Future Directions

There are important limitations to our survey. With any survey, a critical issue is how well respondents represent the target population. Overall, this survey received responses from approximately 10% of academic pulmonologists in the United States. Sampling bias (i.e. bias introduced due to differences in the intended target population and the cohort surveyed) is always present, and effort must be made to reduce its impact. Randomly choosing potential respondents from the target population is ideal, but not always practical. In this survey, sampling was not random; emails were sent to potential respondents based on whether or not their training program provided contact information. However, a large percentage of the general population of interest was surveyed (32%) reducing the impact of sampling bias. A second important issue is the survey response rate. Ideally, 100% of those sampled would respond, but again, this is often impractical, particularly with large, geographically diverse cohorts such as this one. The lower the response rate, the more potential for responder bias (i.e.

those who responded are somehow different from those who did not). Our response rate of 33% is typical of physician surveys published in the medical literature. [23] Finally, there is always the potential for survey questions to be misinterpreted.

It is hoped that the observations in this survey serve as a benchmark for understanding how academic physicians approach the diagnosis and management of IPF. Further, these results may provide guidance to thought leaders involved in physician education and practice guideline development regarding continued educational needs.

Acknowledgement

The authors wish to acknowledge the efforts of the 272 participating pulmonologists, and thank them for taking time from their busy careers to contribute to medical research.

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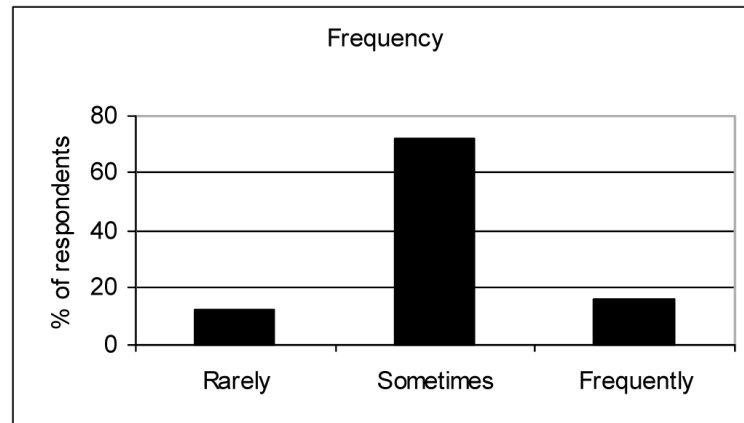
A.**B.**

Figure 1. Figure 1A. Frequency of Acute Exacerbations. Figure 1B. Outcome of Acute Exacerbations.

Figure 1A. Eighty-eight percent of respondents felt acute exacerbations occur “sometimes” or “frequently”.

Figure 1B. Ninety-two percent of respondents felt that acute exacerbations were “sometimes” or “frequently” fatal.

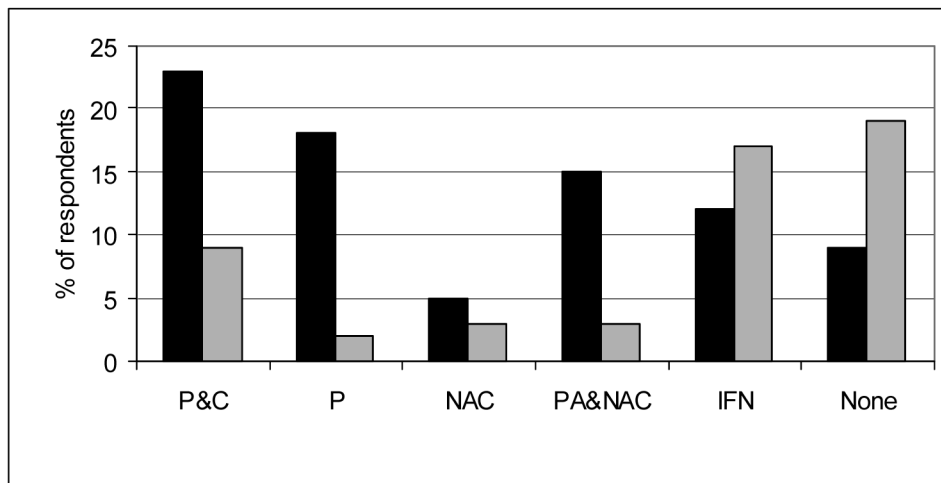


Figure 2. Pharmacologic therapy in IPF

Initial (black bars) and salvage (grey bars) treatment regimens reported by survey respondents (n = 260).

Abbreviations: P&C = prednisone plus cytotoxic therapy; P = prednisone only; NAC = N-acetylcysteine only; PA&NAC = prednisone, azathioprine and N-acetylcysteine; IFN = interferon gamma 1b; None = no therapy.

Table 1

Respondent Characteristics	
Characteristic	Number of Respondents (percent)
Years in practice	
< 5 years	55 (22)
5-15 years	92 (36)
> 15 years	105 (42)
Number of idiopathic pulmonary fibrosis patients seen annually	
None	9 (3)
1-5	93 (37)
5-10	80 (32)
11-20	38 (15)
> 20	32 (13)
Primary academic position	
Clinician educator	105 (42)
Researcher (clinical or basic science)	128 (51)
Administrative	19 (7)
Geographic region of practice	
Midwest	46 (19)
Northeast	54 (21)
South	78 (31)
West	74 (29)

Table 2

Initial Treatment Regimen by Various Subgroups

By Geographic Region	West (n=74)	Midwest (n=46)	South (n=78)	Northeast (n=54)	p value
Prednisone only (%)	23	15	14	19	0.51
Prednisone plus cytotoxic agent (%)	27	17	23	22	0.68
Prednisone, azathioprine, N-acetylcysteine (%)	15	13	19	7	0.29
Any prednisone regimen*	62	37	50	43	0.03
No therapy (%)	4	13	17	4	0.02
By Years in Practice					
	< 5	5-15	> 15		p value
	(n=55)	(n=92)	(n=105)		
Prednisone only (%)	15	15	22		0.36
Prednisone plus cytotoxic agent (%)	20	25	23		0.78
Prednisone, azathioprine, N-acetylcysteine (%)	16	12	15		0.71
Any prednisone regimen*	49	47	52		0.73
No therapy (%)	16	8	8		0.15
By Number of Idiopathic Pulmonary Fibrosis Patients Seen Annually					
	0-5	5-10	11-20	>20	p value
	(n=102)	(n=80)	(n=38)	(n=32)	
Prednisone only (%)	25	19	13	0	0.01
Prednisone plus cytotoxic agent (%)	28	18	29	13	0.12
Prednisone, azathioprine, N-acetylcysteine (%)	5	24	13	22	0.002
Any prednisone regimen*	52	55	47	31	0.14
No therapy (%)	7	6	18	16	0.08

* Any prednisone regimen combines three choices (prednisone only; prednisone, azathioprine; prednisone, azathioprine, N-acetylcysteine)

Table 3

Transplantation by Various Subgroups					
By Geographic Region	West (n=74)	Midwest (n=46)	South (n=78)	Northeast (n=54)	p value
Transplantation (%)	41	70	60	50	0.01
By Years in Practice					
	< 5 years (n=55)	5-15 years (n=92)	>15 years (n=105)		p value
Transplantation (%)	65	60	43		0.01
By Number of Idiopathic Pulmonary Fibrosis Patients Seen Annually					
	0-5 (n=102)	5-10 (n=80)	11-20 (n=38)	>20 (n=32)	p value
Transplantation (%)	41	59	55	81	0.0007