IDIOPATHIC PULMONARY FIBROSIS:
Navigating a Complex Disease In An Evolving Treatment Landscape

EXPERT perspectives

OVERVIEW

Steven D. Nathan, MD, discusses how idiopathic pulmonary fibrosis (IPF) differentiates from other interstitial lung diseases. Dr. Nathan presents the impact of an early and accurate diagnosis of IPF, common symptoms, and the diagnostic tools and criteria used for an accurate diagnosis. In addition, Dr. Nathan reviews the significance of high-resolution computed tomography (HRCT) and what IPF looks like on HRCT scans. Dr. Nathan provides his insights on current treatment options and therapeutic strategies for IPF, which include dosing, monitoring, and common side effects from agents used to treat IPF.

CONTENT AREAS

- Diagnosing IPF
- Differentiating IPF from ILDs
- Symptoms of IPF
- Improving early diagnosis of IPF
- HRCT scan readings
- Treatment options and therapeutic strategies for IPF

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Target Audience
This activity was developed for pulmonologists and other clinicians who may encounter patients with interstitial lung diseases.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Utilize best practices for diagnosing idiopathic pulmonary fibrosis (IPF) in a timely manner
- Differentiate IPF from other interstitial lung diseases
- Compare and contrast current and evolving treatments for IPF
- Identify patients with IPF who may benefit from modifications to their current treatment plan

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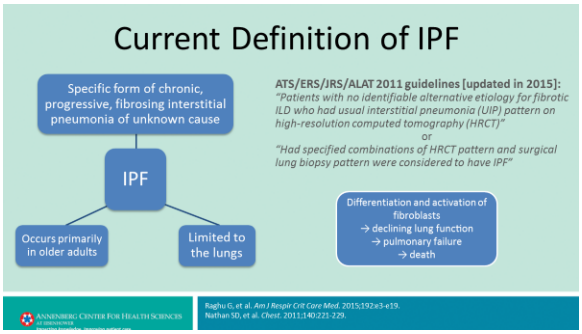
Burden of Disease

In this module, we will review the definition of idiopathic pulmonary fibrosis and discuss its prevalence and how it differentiates from other forms of interstitial lung disease.

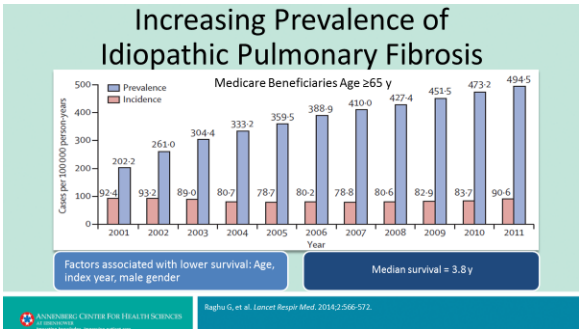
In terms of our current definition of IPF, we define it as a specific form of chronic progressive fibrosing interstitial pneumonia of unknown cause. It occurs primarily in elderly individuals and—for whatever reason—it's limited to the lungs. In terms of our governing body's definition and guidelines—that being the ATS, together with the ERS, JRS and ALAT—they came up with guidelines in 2011, subsequently updated in 2015, where it stated that patients with no identifiable alternative etiology for fibrotic ILD, who have a UIP pattern on HRCT, can be diagnosed as having IPF. Otherwise, if patients don't have a typical appearance of a UIP pattern, in some cases, patients need to go on to have a surgical lung biopsy in order to confirm the diagnosis of IPF. That happens in about 20% to 25% of the cases.

From a pathologic standpoint, what happens that results in this progressive fibrosing disorder, is that we currently believe that it is a disease of the fibroblasts. We have unbridled fibroblastic proliferation. The fibroblasts lay down collagen. The collagen is the scaffold for progressive fibrosis, which results in progressive lung function impairment, ultimately leading to respiratory failure and ultimately resulting in the patient's demise.



In terms of the prevalence and incidence of IPF, we see an increase in this disease, and this has been described not only in North American but in Europe as well. Why we are seeing this increased incidence is really not known. It is a disease of the elderly, and we have a forever aging elderly population. We are getting better at dealing with other diseases, like coronary artery disease, certain forms of cancer, and so, with the aging population, other diseases, such as IPF, are emerging as a disease of the elderly. It is also perhaps increased disease discovery. We are getting many more CAT scans screening for lung cancer and for other reasons, and patients are getting picked up because they are having CAT scans performed for other reasons. So there is certainly increased discovery, as well. And there could be something environmental, or otherwise, that is also resulting in this increasing incidence of IPF. It is a disease of the elderly, as I mentioned, and it also has a high propensity for males, although certainly females can also get this devastating disease.

In various studies that have been done on the natural history of IPF, the survival on average is anywhere from around 3 to 5 years, based on historical data.

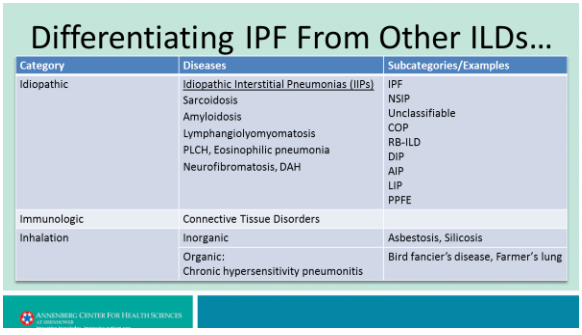


In terms of making a diagnosis of IPF, one first has to differentiate it from other forms of ILD, so it is a diagnosis of exclusion. Depicted here is a mnemonic that some folks find helpful, I certainly do in my clinical practice. And this mnemonic is defined by 5 I's and an N. The "I's" stand for various broad disease categories, and if you remember all these different "I's," then you'll cover most causes of interstitial lung disease.

The first ones shown here are the idiopathics. And under the idiopathics, we have the idiopathic interstitial pneumonias (IIPs) with multiple different disease conditions constituting the IIPs:

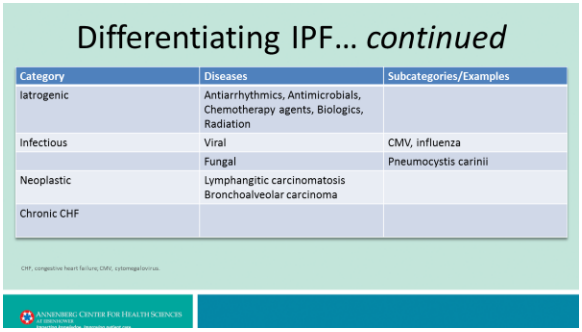
IPF being the most common, NSIP being the second most common, together with the "untestifiables." NSIP is not specific interstitial pneumonia. And then there's an alphabet soup of other conditions, like cryptogenic organizing pneumonia (COP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), lymphocytic interstitial pneumonia (LIP), and PPFE is pleuroparenchymal fibroelastosis. Under the idiopathics you also have other conditions, such as sarcoidosis, amyloidosis, LAM, and others, as shown on this slide.

The second "I" to think of are the immunologic conditions, specifically connective tissue disorders. Things such as rheumatoid arthritis, scleroderma, lupus, mixed connective tissue disease, can all result in interstitial lung disease, and not infrequently, the lung disease might be the first harbinger of an underlying connective tissue disorder. Inhalational conditions or inhalational injuries can also result in interstitial lung disease. Think of asbestosis silicosis and then also chronic hypersensitivity pneumonitis, which is sometimes very difficult to differentiate from IPF.

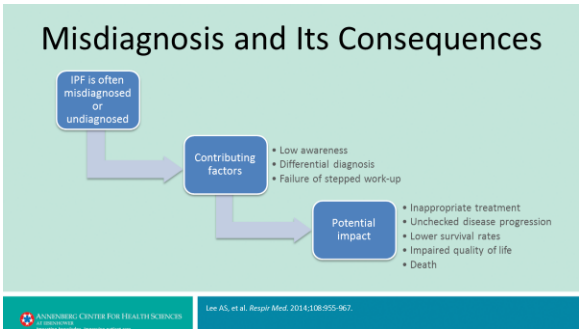


The next are the iatrogenics, what we as physicians and providers impose on our patients in terms of medications. Certain anti-arrhythmics like amiodarone, chemotherapeutic agents, and certain radiation can all result in fibrosis. The fifth "I," to complete the story, are infections. Certain viral infections, fungal infections, like PJP [pneumocystis jiroveci pneumonia], can give you diffuse interstitial infiltrates.

The "N" stands for neoplasms. There are certain . . . some are granuloplasm like intragenic carcinomatosis or bronchoalveolar carcinoma that can present with interstitial infiltrates. Sometimes we add a "C" onto the mnemonic, so 5 "I's," a "C," and an "N," for chronic congestive heart failure, although that's usually pretty evident and easily differentiated from interstitial lung disease.



IPF is oftentimes misdiagnosed and undiagnosed. If you think about this and why this is, it's a disease that typically presents with shortness of breath, plus or minus a cough, and it's competing against other much more common conditions that can present with the same symptoms. So if you think about the overall prevalence of IPF in the USA, it's around 125,000, maybe close to 200,000, and then you think of other conditions like COPD, where there are about 20 million in the US; asthma, another 20-25 million; chronic congestive heart failure another 5 million. So, for any primary care physician who makes a diagnosis of CHF or COPD, they're going to be right 95%-99% of the time. The key is to discriminate and differentiate interstitial lung disease from these other more common causes of shortness of breath. So, there is certainly low awareness. It's competing with these other more common conditions in terms of a differential diagnosis. The impact might be that patients are misdiagnosed, receive inappropriate treatment, and the disease might progress while they await the appropriate diagnosis being made. This can certainly impact survival rates, quality of life, and perhaps lead to patients' earlier demise than would have been otherwise if they had been picked up earlier.



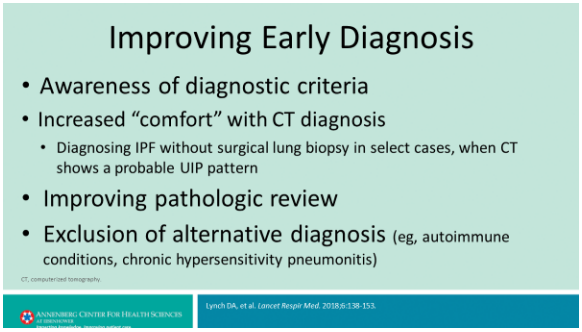
Diagnosing IPF

In this module, we will discuss how to diagnose IPF, common symptoms, and the diagnostic tools and criteria used for an accurate diagnosis. In addition, we will discuss what to look for in pulmonary function tests and how to measure disease severity.

There needs to be an increased awareness of IPF, as well as a focus on improving the early diagnosis of IPF. Inherent to this, is that there needs to be a greater awareness of the diagnostic criteria in order to attain an accurate diagnosis of IPF. This includes an increased comfort level with the CT diagnosis. As CT technology evolves, I think more pulmonologists and radiologists are developing more comfort in making a diagnosis of IPF without the need to go on to surgical lung biopsy in as many cases as we did maybe 10 or 20 years ago.

The CT needs to show a UIP pattern, or probable or possible UIP pattern, to make the diagnosis of IPF. Even if a patient has a possible UIP pattern, in the appropriate clinical setting, that might be sufficient to make a diagnosis of IPF. An appropriate clinical setting might be, for example, a 75-year-old male, a former smoker, who doesn't have any exposures, no underlying stigmata of a connective tissue disease—the likelihood is very high that patient has IPF. And you put that together with a possible UIP pattern, that might be enough to clinch a diagnosis of IPF.

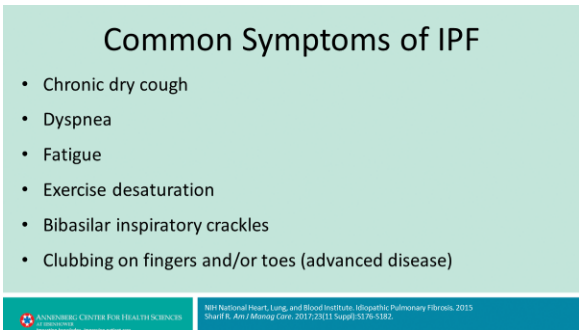
About 20%-25% of patients will go on to require a surgical lung biopsy and a pathologic review. There needs to be an increased understanding and awareness of what a UIP pattern looks like histopathologically. Incumbent in the work-up of patients is the exclusion of other conditions, such as autoimmune conditions, as well as chronic hypersensitivity pneumonitis, which can both mimic IPF.



The common symptoms of IPF include a dry cough; this can be a chronic hacking dry cough. In about 10% to 15% of cases, this is the only symptom and it can pre-date the onset of the shortness of breath. So, when a clinician is faced with a chronic cough, things they typically think of might be asthma, might be a postnasal drip, might be gastroesophageal reflux disease, might be a bronchitis. It's easy to understand why patients will go misdiagnosed if they present only with a chronic cough.

Dyspnea, I alluded to already, in terms of competing with COPD, heart failure, asthma, deconditioning all of these things can present with dyspnea. Fatigue is usually more of a late-term type of presentation. When the patient starts to desaturate, then they might develop some fatigue associated with this as well. What can happen in any patient with any disease who has shortness of breath, they tend to do less. The less they do, the more fatigued they become. They become deconditioned, and they get into this spiral of shortness of breath, leading to more fatigue, leading to further deconditioning. Exercise desaturation invariably steps in as the disease progresses, and a big clue on physical exam is the presence of bibasilar inspiratory crackles, which have been described as Velcro-like in nature because they sound like Velcro being pulled apart. It's unusual, but you can see clubbing of the fingers. This is really a nonspecific sign; it can be seen in other

conditions, as well. I think today we see less clubbing, as we pick up on hypoxemia earlier than we did perhaps 20 or 30 years ago.

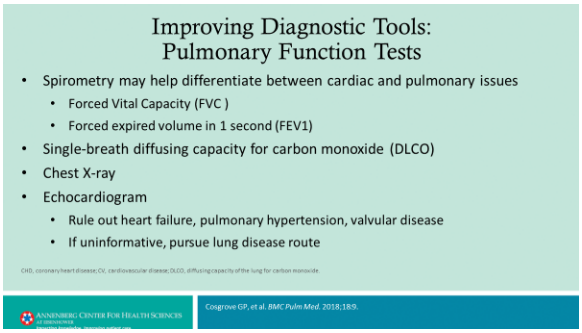


Pulmonary function studies are an important tool to help us diagnose restrictive lung disease, with IPF being one of the forms of restrictive lung disease. Spirometry can be misinterpreted, and it's very important to be aware of the difference in what you might see on spirometry between COPD, asthma— which are obstructive conditions—and IPF and interstitial lung disease, which are restrictive conditions. In asthma/COPD you see a disproportionate reduction in the FEV1 compared to the FVC, so that the FEV1:FVC ratio is typically low, at least less than around 70%. In IPF, both the FVC and FEV1 decrease proportionate to one another, so that the FEV1:FVC ratio is normal or, in some cases, might actually be increased. It's another very important point that normal lung function does not exclude interstitial lung disease in IPF. You can have patients with significant fibrotic lung disease and lung function studies that are in the normal range.

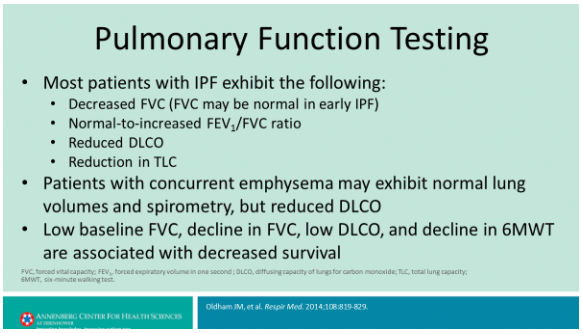
A single breath diffusion capacity for carbon monoxide is invariably reduced. I don't recall seeing many, if any, patients with IPF that is well established, with a normal DLCO.

The chest X-ray provides an important clue as to the presence of interstitial lung disease. You can see diffuse increased interstitial markings. You might see reduced lung volumes consistent with the restrictive process, and this is the step, typically, that we will do before we go on to the HRCT, which provides further and better definition of the lung parenchyma. Frequently, when these patients present with dyspnea, cardiac etiology will always be in the differential. A good screen is an echocardiogram to rule out heart failure, to check what their ejection fraction is, to make sure that they don't have evidence of any diastolic dysfunction, valvular disease, or pulmonary hypertension.

So, frequently, many of these studies are obtained concomitantly before the clinician looks at them all to make a decision where next to go in terms of a diagnostic algorithm.

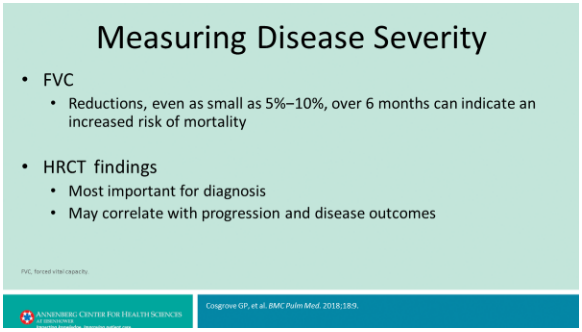


So, most patients with IPF, I've alluded to this already, present with a decreased FVC and reduced DLCO. The total lung capacity tends to track the FVC. Don't be fooled, once again, if the patient presents with normal lung volumes, especially in patients with concurrent emphysema. In about 30% of IPF patients, there can be concomitant emphysema, and then we have a distinct entity of combined pulmonary fibrosis and emphysema with CPFE. These patients very typically present with normal lung volumes but a severely reduced diffusion capacity. The reason for the normal lung volumes is because IPF tends to be a restrictive process that causes the lung volume to go down. Whereas, COPD, an obstructive process, causes the lung volumes to increase. So, you have opposing mechanical forces, which at the end of the day result in normal lung volumes being seen. A low diffusion capacity, a low FVC, a decline in FVC, a decline in the 6-minute walk test, are all biomarkers associated with a reduced likelihood of survival. These are physiologic biomarkers that tell us that patients potentially will do poorly.

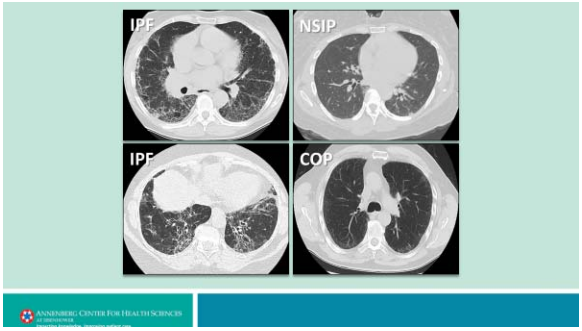


With regards to the FVC, which is the most closely of the physiologic markers that is followed, typically a reduction of around 10% portends the worst prognosis, with an increased mortality. But there is data that shows that even reductions as small as 5% over 6 months can indicate a worse outcome.

HRCT is very important for making a diagnosis. It's not quite as good for following the course of the disease, although, typically, in our practice, we will get a CT at least once a year. There are some tools out there to provide more objective software-driven measurements of the burden of parenchymal lung disease on HRCT, but none of those are really used in the clinical arena and are mostly in a research setting, at this time. The reason that we obtain CTs on an annual basis is that some of these patients can have their course complicated by the occurrence of lung cancer. And about 5% or 10% of patients with IPF will [actually] succumb from lung cancer.



Here we have an example of 4 different CTs. The 2 showing to the right were treated with prednisone, with steroids, and they got distinctly better. That was a case of cellular NSIP. This was a case of cryptogenic organizing pneumonia. The 2 on the left are more fibrotic and didn't respond to the steroids, not that they should have been given steroids, and these are both cases of IPF.



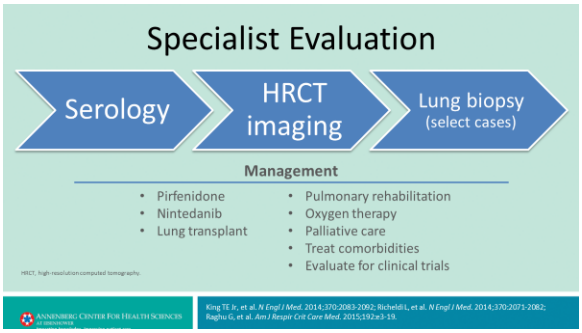
In terms of when these patients see a specialist—a pulmonologist—what is the typical evaluation that takes place? The patient has been screened for the shortness of breath and cough. There is some kind of interstitial lung disease. The HRCT may have been obtained or not. Typically, along the way, they will get serologists to rule out an underlying connective tissue disease. The HRCT is really the central diagnostic modality that determines where to go next. Sometimes one can stop at the HRCT and say this is a UIP pattern, and I believe this patient has IPF, or this is a possible UIP pattern. But because the patient is 75 years old, a former smoker, and there is nothing else going on, the likelihood is very high to make a diagnosis of IPF, and therefore . . . I'll stop right there. But, as pulmonologists, when we see these patients, we have to take into account the global care and global management, and it's not just making a diagnosis, but coming up with a management plan thereafter.

Management might include one of the antifibrotic agents, either pirfenidone, and nintedamib.

If they're young enough, robust enough, without significant comorbidities, they might potentially be candidates for lung transplantation. So, work-up for lung transplantation can never be too early in IPF because of the unpredictable nature of the disease. What I typically say to patients is, let's hope for the best, but prepare for the worst. Let's hope you stay stable, but let's prepare for the event that you might have a decline at any time, by putting a

lung transplant evaluation in place as a final safety net.

Pulmonary rehab is very important for all patient as the disease progresses. Invariably, most of them will require oxygen therapy at some point. Palliative care also becomes important for symptom control, as does hospice, as patients head towards the later stages of their disease. We should also be on the lookout for comorbidities, which might affect their quality of life, as well as potentially impact on their mortality. And then, even though we have 2 drugs available to treat IPF now, we've still got a ways to go. Patients should be offered the opportunity to be evaluated for enrollment in clinical trials.



HRCT Presentation

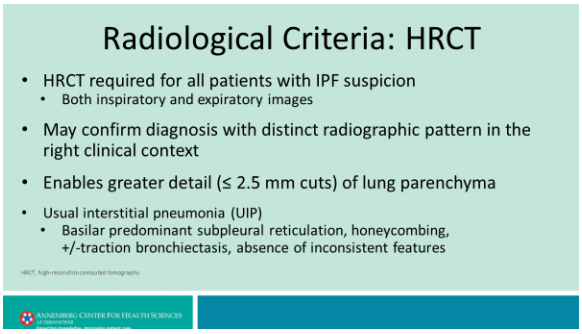
In this module, we will discuss the significance of HRCT, how IPF patients present, and what IPF looks like on HRCT. We will also discuss when to consider surgical lung biopsies and common pathologic reviews. And, last, we will talk about the importance of multidisciplinary collaboration and review of common comorbidities.

HRCT is required for all patients who have interstitial lung disease where there is a suspicion of IPF. It's typically helpful to have both inspiratory and expiratory images. Expiratory images are helpful to rule out air trapping, which can be seen with chronic hypersensitivity pneumonitis, which is one of the mimickers of IPF. If there is a distinctive radiographic pattern in the appropriate clinical context, it might be enough to make a diagnosis of IPF. So, you can have a UIP pattern, or you can have a possible UIP pattern. A possible UIP pattern by itself is not enough to obtain a diagnosis, but together with the right clinical presentation, it could be sufficient to obtain a clinical diagnosis of IPF.

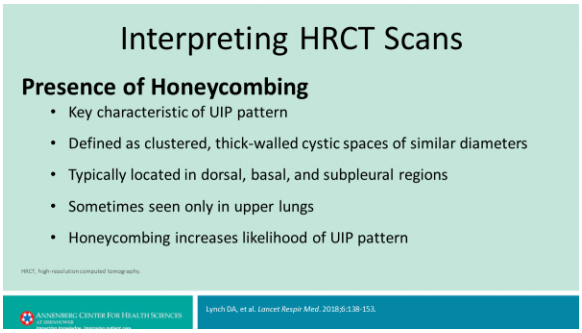
By way of example, a correct clinical situation or appropriate clinical situation might be a 78-year-old Caucasian male, former smoker, who doesn't have any other exposures, who has crackles at his bases, and has a possible UIP pattern—if you put that constellation of the clinical together with the radiographic, that might be enough to obtain a diagnosis of IPF without necessarily going on to surgical lung biopsy.

The HRCT provides greater detail over the lung parenchyma in terms of the cuts, which are typically less than around 2 mm. And you can see the definition, which enables you to pick up the subpleural reticulation, the honeycomb cysts, the traction bronchiectasis better than a regular CT, which doesn't quite give you that level of definition.

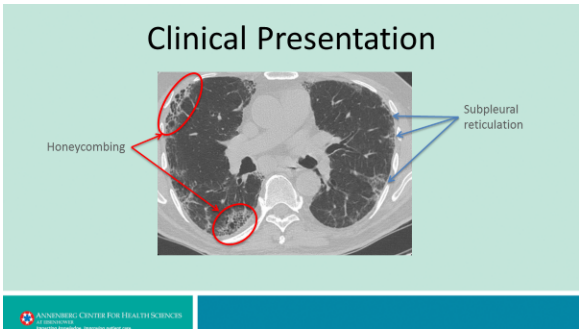
A UIP pattern is characterized radiographically on HRCT by basilar predominant subpleural reticulation, the presence of honeycombing with or without traction bronchiectasis, and the absence of inconsistent features. Inconsistent features might be cysts, ground-glass opacification, nodules, consolidation. If you have any of these or too much of these, then that would make the CT inconsistent for UIP pattern or perhaps—new terminology that's coming out— indeterminate for a UIP pattern. If you lack honeycombing, but you just have subpleural reticulation, that would be regarded as a possible UIP pattern, or more recently, a probable UIP pattern.



Honeycombing is a key characteristic of the UIP pattern. These are defined as clustered thick-walled cystic spaces of similar diameter. Usually you see them stacked up at least in 2 rows. Sometimes 1 row is sufficient to make the diagnosis of honeycombing. Usually, it hugs the baseline, or the subpleura, of the lungs in order to be regarded as honeycombing of IPF. Occasionally, it might only be seen in the upper lobes. Certainly, the presence of honeycombing in the appropriate clinical context increases the likelihood of a UIP pattern and a diagnosis of IPF.

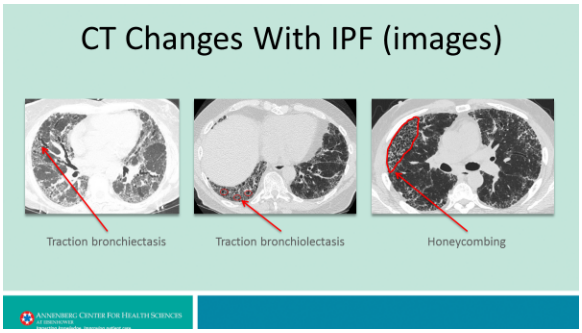


Here we have an example, shown very nicely, of subpleural honeycombing. You can see the rows of the cysts stacked up with one another, both anteriorly and posteriorly, both very good examples of honeycombing. Here we see—marked with the blue arrows— subpleural reticulation. We shouldn't see these little lines coming out from the pleura. Typically, about the lateral one-third of the lung lacks markings in a normal patient, because there is a paucity of vasculature this far out in the lungs. So, this is certainly abnormal. And this kind of CT between the subpleural reticulation and the honeycombing might be sufficient to make a diagnosis of IPF in the appropriate clinical context.



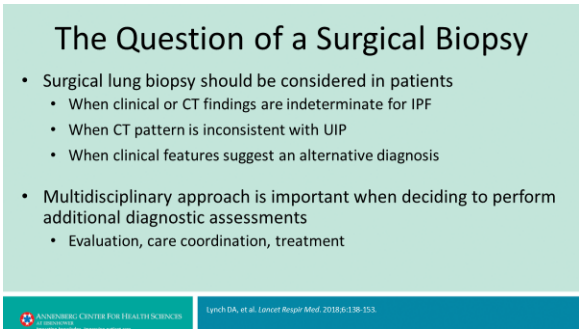
That was a good example of what IPF might look like on a HRCT. The reticular pattern that I showed is a network of fine lines that are irregularly spaced with both a mix of thicker and thinner lines. Traction bronchiectasis is basically the airways getting pulled apart by the fibrotic process. You don't have to have traction bronchiectasis to make the diagnosis of IPF. And it may or may not be seen in any given patient with IPF. It can sometimes be quite difficult to distinguish honeycombing from traction bronchiectasis specifically traction bronchiectasis, which is pulling apart of the smaller airways which tend to occur out in the periphery where honeycombing tends to occur, as well.

Here we have some more examples of CT changes with IPF. This is a very nice example of traction bronchiectasis shown with the red arrow. This is traction bronchiolectasis, so the same kind of concept: airways being pulled apart, but bronchiolectasis are the smaller bronchioles. When you see them end on, they can look very similar to the honeycombs cysts, but you can get a sense that they're not clustered together. This is traction bronchiolectasis, and they're not hugging the pleura like we see with honeycombing. This is a nice example of a good patch of honeycomb cysts subpleurally.



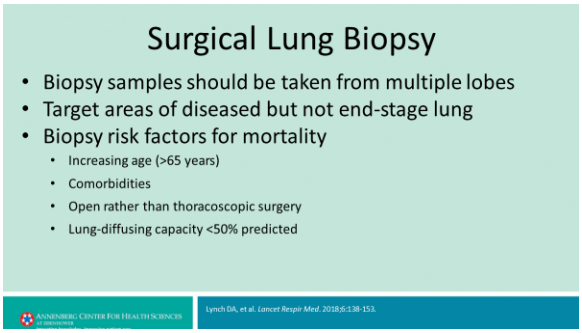
The question often comes up as to whether patients should get a surgical lung biopsy or not. Surgical lung biopsy might be indicated in certain patients where, after you put the clinical together with the radiographic, you still are uncertain as to whether this could be IPF or something else. Especially if there are features to suggest an alternative diagnosis, then a surgical lung biopsy would be indicated. For example, NSIP. Very rare, very

unusual to make a diagnosis of NSIP without a surgical lung biopsy. Multidisciplinary approach is important when deciding to perform a surgical lung biopsy, and certainly in the interpretation of the surgical lung biopsy, and is also very important in the care and coordination of the patient's management plan.

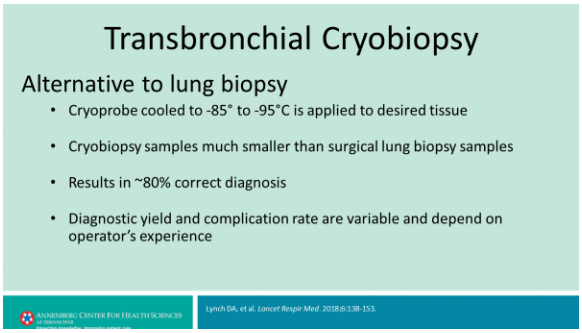


When a biopsy is taken, the surgeon needs to be aware that he or she should be taking biopsies from multiple sites, at least from 2 lobes, and preferably from 3 lobes. The surgeon should stay away from the areas that are most diseased, because if you get a lung biopsy that just shows advanced fibrosis with nothing else, it's going to be very difficult to discern a distinct entity from another distinct entity. All of these fibrotic lung diseases can progress to end-stage fibrosis. If the lung biopsy only shows end-stage fibrosis, without any other features of UIP, then you might miss the opportunity to make a diagnosis of IPF.

There is certain risk with any invasive procedure, including surgical lung biopsies or VATS lung biopsy, so you have to pick your patients quite carefully. But in the appropriate hands, with well-vetted patients, it is a pretty low-risk type of procedure.

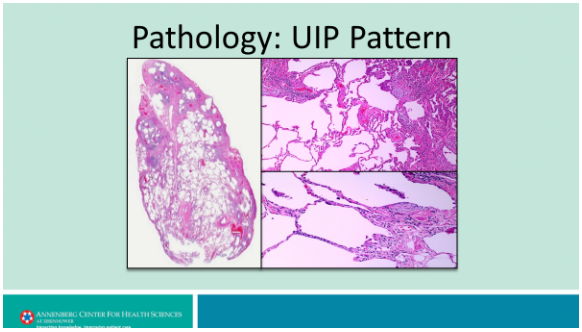


At some centers, there's more of a comfort zone with cryobiopsies. Cryobiopsies obtain big chunks of tissue bronchoscopically. Whether or not this is quite as good as a surgical lung biopsy, there haven't been any really good prospective studies comparing a VATS biopsy to a cryobiopsy. But it appears that it can help the diagnostic yield, and certainly is better than a transbronchial biopsy, and might provide enough tissue—in the appropriate clinical context and radiographic appearance—to make an accurate diagnosis of IPF.

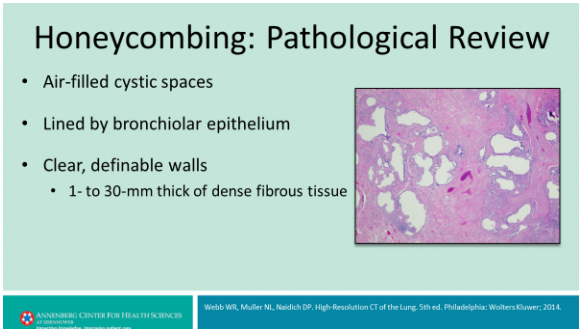


What does UIP look like pathologically? Here we have a UIP pattern under low power. A lot of times you can have a fair idea, even under low power, that you're dealing with a UIP pattern. The first thing to note is the heterogeneity. What we mean by that is different things happening in different parts of the lung. Here you see more normal alveolar within the center of the lung. You get a sense that there is subpleural fibrosis, all that pink shown towards the right is subpleural fibrosis. And then you see microscopic honeycomb cysts amongst the subpleural fibrosis. So, right away, when you see this under low power, you are strongly suspicious that this might be UIP.

As you go under higher power, you see the transition between normal and abnormal lung. It's usually, or oftentimes, a sharp demarcation between what we are seeing was thin-walled alveolar sacs (towards the lower left side of this particular photograph), and more dense fibrosis up towards the upper right panel, between 12 o'clock and 3 or 6 o'clock. Under even higher power, the bluish areas of cells you can see, these spindle-shaped cells, are the fibroblasts. They typically occur in foci altogether. And a lot of times we'll see these fibroblastic foci at the interface between normal and abnormal lung. So, this is the marching front of the disease. It's the fibroblasts that lay down the collagen that subsequently goes on to form the fibrosis.

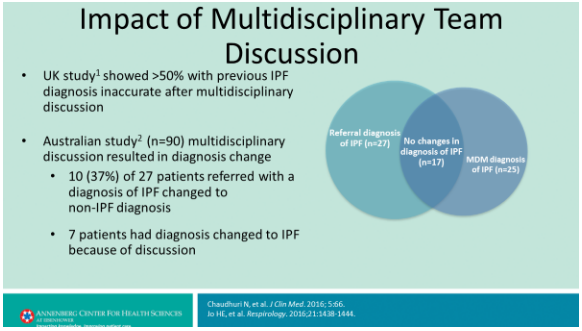


Here we see microscopic honeycombing. You can see the cysts within dense fibrosis. Typically, the line of the bronchial epithelium, and they can vary in their size, as well as how many occur together. They can occur like pools of water, so to speak, or lakes seen at a distance. This is a good example of honeycomb cysts.



In terms of the multidisciplinary collaboration to make as accurate a diagnosis as possible, that involves a discussion between the pulmonologist, who provides the clinical background; the thoracic radiologist, who can provide the fine detail of the chest HRCT; and in those cases that need a surgical lung biopsy, the pathologist will weigh in with the pathologic features. It takes a group discussion between all 3 disciplines—and others that might be present there, sometimes a rheumatologist as well—to make as accurate a diagnosis as possible.

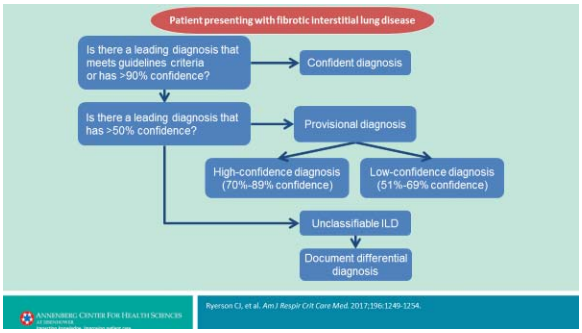
There have been studies looking at the impact and influence of multidisciplinary team discussions. What has been seen in a number of studies is that in expert centers who run these studies, frequently the diagnosis is changed to one of IPF or changed from one of IPF to another disease condition. So, even though it seems self-serving, from someone who works at one of these centers, we do encourage all patients to be seen at least once at an ILD specialty center to make sure that the appropriate diagnosis has been made.



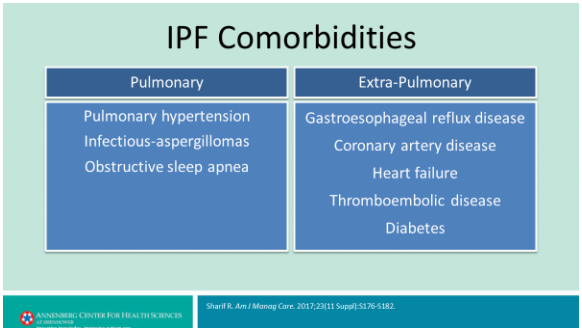
It can be difficult, even at expert centers, for patients presenting with any form of fibrotic interstitial lung disease, to make an accurate diagnosis. This was taken from a recent paper that provides an algorithm that I think is helpful to all

of us who are in the clinical trenches. First of all, the way this leads us, is whether or not there is a leading diagnosis that meets guideline criteria for confident diagnosis. And when we say confident, greater than 90% likelihood that this is the disease we are dealing with. If that is the case, you can make the diagnosis.

But what about those cases where the level of confidence isn't quite the same? Where you're suspicious of IPF, for example. If you have a greater than 50% likelihood that the patient has this diagnosis, you can provide a provisional diagnosis with either high confidence or low confidence shown in the 2 categories here. If you are 70%-90% certain that this is the disease, you can make a provisional diagnosis of, for example, IPF. If you only have low confidence in the clinical features, the radiographic and the pathologic, then you can make a provisional diagnosis with low confidence. If you're not confident at all, and there is a less than 50% chance you are dealing with IPF, or any other specific disease entity, then you might be left with this very broad wastebasket term of "unclassifiable" interstitial lung disease.



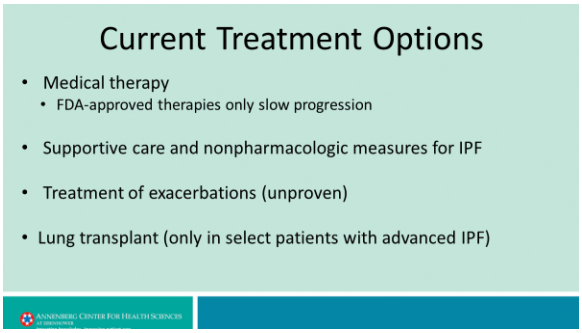
It's important in the global holistic care of these patients to be aware of, and focus on, ruling out and managing potential comorbidities. Pulmonary hypertension can complicate the course of patients with IPF. Aspergillomas are extremely rare. Obstructive sleep apnea is extremely common and is something that patients should be screened for. There are extrapulmonary comorbidities, including GERD—extremely common. Coronary artery disease is more common in IPF, even if you control for risk factors, like smoking and age, CAD is more common. As is heart failure, thromboembolic disease, and even diabetes has a 2-fold increased prevalence in patients with IPF.



Therapeutic Strategies

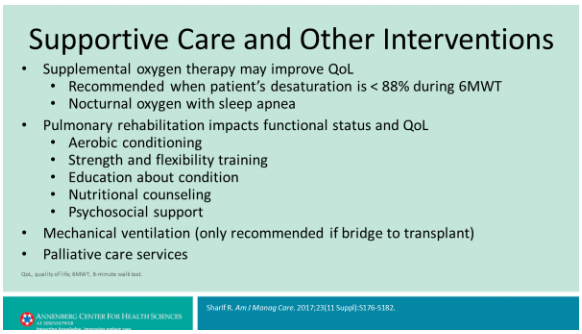
In this module, we will discuss current treatment options and therapeutic strategies for IPF, as well as dosing, monitoring, and common side effects from agents used to treat IPF. We will also discuss the significance of, and data from, the Pulmonary Fibrosis Foundation Patient Registry. We'll talk about the latest data on emerging therapies and review key takeaways from this presentation.

In terms of current treatment options, there are 2 FDA-approved therapies: both work to slow disease progression. Neither of them are a cure. In addition to these therapies, there are other management strategies, including supportive care and other nonpharmacologic measures for patients with IPF. Some of these patients will have their course complicated by the development of acute exacerbations, but therapy for this is mostly unproven, and the course—once patients develop a true acute exacerbation—the course tends to be pretty dismal, with a very poor prognosis once this sets in. Lung transplantation is available for select patients who have advanced IPF, provided they are young enough and don't have limiting comorbidities that might preclude their lung transplant candidacy.



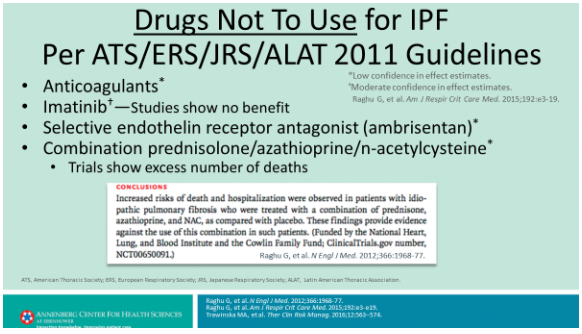
In terms of supportive care, supplemental oxygen is something to consider in those patients who have significant and sustained desaturation, be it with exercise or nocturnal desaturation. Pulmonary rehab is something that all patients with IPF can and will benefit from, as the disease progresses and as they become more impaired in terms of their shortness of breath. Pulmonary rehab includes education, aerobic conditioning, strength and flexibility training, education/nutritional counseling, psychosocial support—these are all very important components of a comprehensive pulmonary rehab program.

As patients head towards the late stages of their disease, mechanical ventilation is really futile care, in my opinion, unless the patient is being considered as a potential lung-transplant candidate. If patients, or ideally before patients get to this point, palliative care services and hospice should be brought in for discussion, and a transition of these patients to more of a comfort-care type of situation.



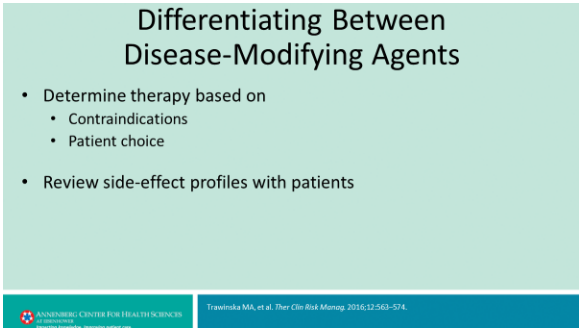
The governing bodies, including the American Thoracic Society, European Respiratory Society, mostly therapies have come out with guidelines in terms of therapies to use and therapies not to use in patients with IPF. Unfortunately, most of these therapies not to use—including anticoagulation, unless the patient warrants anticoagulation for another reason. This is based on the ACE study [Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis] of Warfarin that showed that this was actually harmful with increased hospitalization, increased mortality, in patients with IPF.

Imatinib has also been studied in IPF. There is no benefit to this. All 3 ERAs (endothelin receptor antagonists) have been studied in IPF without any benefit, including ambrisentan, bosentan and macitentan. Then, a message that still needs to get out more, is the role, or lack of a role, for immunosuppressive therapy in the form of prednisolone and azathioprine. Prednisone and azathioprine were recommended as recently as 13 or 14 years ago. Sorry, let me do my math again. More like 2 decades ago, we were recommending azathioprine and prednisone. It has since been shown through the PANTHER study, that not only does prednisone and azathioprine not work, but they actually are harmful. They are harmful to patients with IPF with increased hospitalization and mortality from these 2 agents. These were studied together with N-acetylcysteine. N-acetylcysteine by itself, neither helps nor hurts patients with IPF, so not something that's recommended—but at least it's not harmful!



When we talk about the antifibrotics, or disease-modifying agents, we are referring to nintedamib and pirfenidone. Both of them were approved in October 2014, and it's nice to have a choice. We went from having nothing, to having a choice

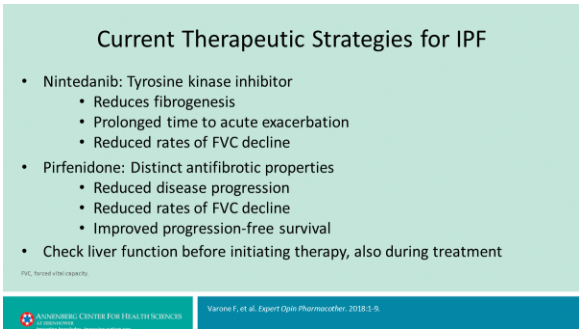
between the 2. How do we choose between these 2 different agents? Well, we try and pick the one that's most suited to the patient's lifestyle, that they're most likely to tolerate, and they're most likely to be compliant with. Because the key to success with both these agents is to maintain patient compliance and to continue the patient on either of these 2 therapies.



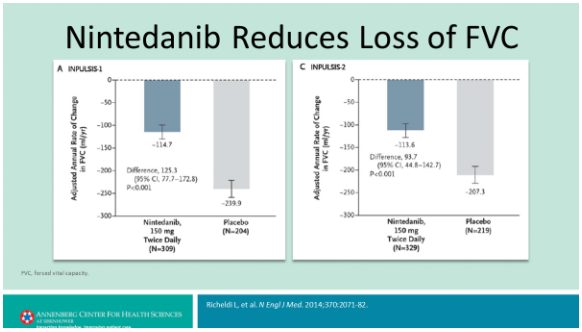
Nintedamib, first, is a tyrosine kinase inhibitor. It reduces fibrogenesis. It's been shown to delay the time to first acute exacerbation, as well as to reduce the rate of decline in the forced vital capacity (FVC).

Pirfenidone has distinctive antifibrotic properties. It also delays disease progression by delaying the decline in the FVC with an improved progression-free survival (PFS).

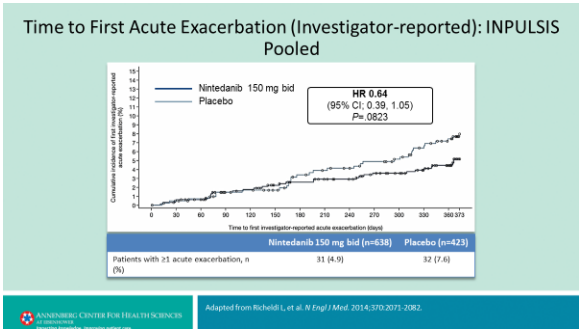
Both of these drugs might have side effects—not everyone gets them. One of the side effects can be transaminitis; and so, therefore, it's very important to obtain baseline LFTs; to check them monthly, initially, and then every 3 months thereafter to make sure that the AST and ALT are not increasing. With that said, there have been no reported deaths from liver failure. No reported liver transplants as a result of any LFT abnormalities that might occur with either of these 2 agents.



This is the data from nintedamib. The 2 phase 3 studies that enabled this drug to be approved were INPULSIS-1 and INPULSIS-2, which both showed consistently that the drug delayed the rate of decrement in the FVC compared to the placebo arm.

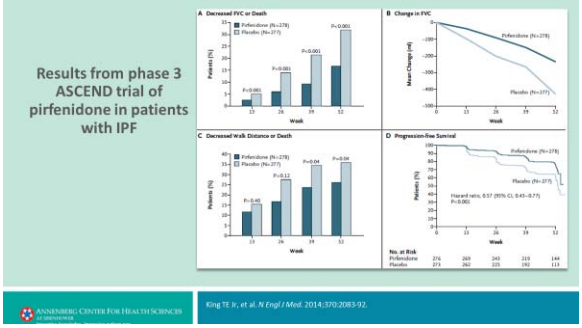


This is also data from 3 studies pooled together, sorry 2 studies—the 2 INPULSIS studies—showing, or testing to, a delay in time to first acute exacerbation in patients with IPF who were treated with nintedamib.

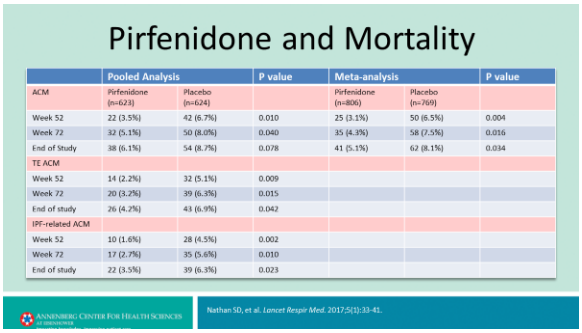


Moving on to pirfenidone, there were 3 phase 3 studies that enabled this drug to be approved. The third of these was the ASCEND study, and this is data from the ASCEND study showing very similar

data to what I showed with nintedamib. Mainly, a delay in progression of disease as manifest by the FVC, as well as other secondary endpoints, including the 6-minute walk and then the composite of FVC or death where there was a delay, or improvement in the progression free survival.

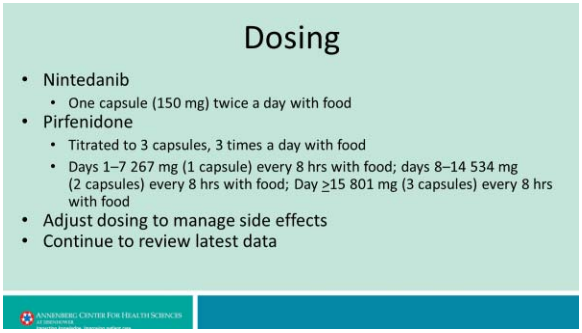


There was also data . . . this is a post-arc analysis suggesting or showing that pirfenidone does impact mortality. All-cause mortality (ACM) was looked at. Treatment-emergent all-cause mortality (TE ACM) was looked at. IPF-related all-cause mortality was looked at, as well. To me, the most clinically useful of these is treatment-emergent all-cause mortality, because these are the patients who went on pirfenidone and stayed on pirfenidone, as opposed to all-cause mortality, which was intent-to-treat. Intent-to-treat means that the patients got the pirfenidone for 1 week and came off, or 2 months and came off; they were still analyzed in the pirfenidone arm. What we, as clinicians, want to know, is if we put patients on a drug and manage to keep them on a drug, what the outcomes are going to be. And you can see that there was a significant mortality benefit all the way through the end of the 3 combined studies: the 2 CAPACITY studies and the ASCEND study. There is also meta-analysis from the same paper combining the 3 studies that I just mentioned, with 2 Japanese studies showing through this meta-analysis that there was a survival benefit to pirfenidone.

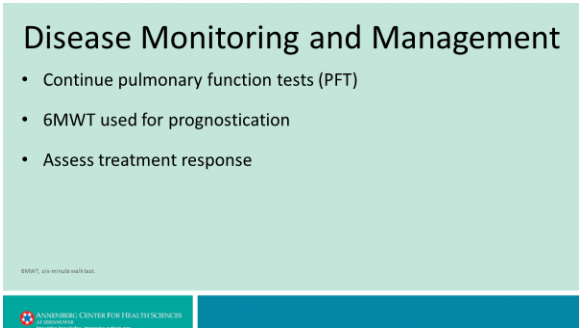


	Pooled Analysis		P value	Meta-analysis		P value
ACM	Pirfenidone (n=623)	Placebo (n=624)		Pirfenidone (n=806)	Placebo (n=769)	
Week 52	22 (3.5%)	42 (6.7%)	0.010	25 (3.1%)	50 (6.5%)	0.004
Week 72	32 (5.1%)	50 (8.0%)	0.040	35 (4.3%)	58 (7.5%)	0.016
End of Study	38 (6.1%)	54 (8.7%)	0.078	41 (5.1%)	62 (8.1%)	0.034
TE ACM						
Week 52	14 (2.2%)	32 (5.1%)	0.009			
Week 72	20 (3.2%)	39 (6.3%)	0.015			
End of study	26 (4.2%)	43 (6.9%)	0.042			
IPF-related ACM						
Week 52	10 (1.6%)	28 (4.5%)	0.002			
Week 72	17 (2.7%)	35 (5.6%)	0.010			
End of study	22 (3.5%)	39 (6.3%)	0.023			

In terms of the dosing, nintedamib is given as 1 capsule, twice a day. It's important for both of these drugs to be taken with food. Pirfenidone is initially started and titrated up to 3 tablets, 3 times a day. There is a formulation: if the ipatients are able to get to 3 tablets, 3 times a day, where they can get converted to 1 tablet 3 times a day, which provides the same dose.



Once the patients are in therapy, we continue to follow them with PFTs, 6-minute walk. And it's important to track them and counsel them if they should develop any side effects, which might require dosing interruptions or dosing modifications.



The side effects of the 2 drugs are shown here. Both of them can cause GI side effects. The main one with nintedamib is diarrhea. But certainly, GI side effects can occur with pirfenidone, as well. Pirfenidone can be complicated by the development of a rash or photosensitivity rash, so patients need to be counseled about using appropriate block out when they go out in the sun. There's a very small signal of increased myocardial infarcts from nintedamib, as well as a very slight signal of increased bleeding with nintedamib. So, word of caution about patients who are on anticoagulation for other reasons. And then I mentioned the potential for transaminitis from both drugs.

Common Side Effects

	Pirfenidone	Nintedanib
Gastrointestinal	Anorexia (8%), nausea (20%), dyspepsia (12%), vomiting (7%), diarrhea (6%), weight loss (5%)	Diarrhea (44%), nausea (17%), vomiting (9%), GI perforation (0.3%)
Dermatologic	Rash (20%) Photosensitivity (8%)	
Cardiovascular		Myocardial infarction (1.1%)
Hematologic		Bleeding events (3%)
Hepatic	Transaminitis (2.5%)	Transaminitis
Embryofetal toxicity		Yes

King TE Jr., et al. *N Engl J Med.* 2014;370:2083-2092.
Richeldi L, et al; INPULSIS Trial Investigators. *N Engl J Med.* 2014;370(22):2071-82.

The Pulmonary Fibrosis Foundation has created a patient registry, which has been around since March of 2016. The goal is to get at least 2000 patients into this registry to learn more about the natural history of IPF, as well as other forms of interstitial lung disease, from across a wide geography, as well as with wide ethnic disparity, to look for any differences in how IPF might behave in certain areas and amongst certain groups.

Pulmonary Fibrosis Foundation Patient Registry

- Goal: Create cohort of well-characterized patients for participation in retrospective and prospective research.
- Registry enrollment began in March 2016
- As of March 31, 2017 (n=767)
- Targeting 60% IPF patients of 2,000 goal of ILD participants across 40 clinical sites
- The PFF Patient Registry is actively enrolling participants.

ILD, interstitial lung diseases.

Flaherty KR, et al. Pulmonary Fibrosis Foundation Patient Registry. Pulmonary Fibrosis Foundation. 2017.

This is some initial data that has come out from the registry where it looks like this is very representative of IPF patients in general. In the registry, these patients have mild restriction, with FVCs in the 67% to 68% range, maybe mild-to-moderate restrictive disease. Just under half of them are using home oxygen already. They do have comorbidities. Very frequently these patients with IPF will have multiple comorbidities that need to be addressed. And then what's interesting from this analysis is that of those patients with IPF, about two-thirds of them were receiving antifibrotic therapy. Arguably, I'm not sure why, one-third of them were not; might have been patient choice. I think perhaps, as a group, we need to be doing a slightly better job than two-thirds of patients on antifibrotic therapy, since there are potentially more patients who can benefit from going on either nintedamib or pirfenidone.

PFF Data Results

Variable	IPF n=448	non-IPF n=319	p-value
Consented Biorepository	93%	89%	0.11
Age, years	70 (8)	64 (12)	<0.01
Male	74%	45%	<0.01
Former Smoker	66%	50%	<0.01
Pulmonary Function			
FEV_1, % pred	71 (17)	70 (20)	0.39
FVC, % pred	67 (17)	68 (19)	0.81
DLCO, % pred	41 (18)	45 (18)	<0.01
Home oxygen use	45%	43%	0.64

Variable	IPF n=448	non-IPF n=319	p-value
Comorbidity			
GERD	64%	55%	0.02
Sleep Apnea	29%	27%	0.45
Depression	17%	16%	0.60
Anxiety	10%	16%	0.03
Coronary Artery Disease	24%	17%	0.02
Medical Therapy			
Immunosuppression, any	4%	59%	<0.0001
Antifibrotic	65%	5%	<0.0001
N-acetylcysteine	3%	1%	0.14

PFF, Pulmonary Fibrosis Foundation; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, diffusing capacity of lungs for carbon monoxide.

Adapted from Flaherty KR, et al. Pulmonary Fibrosis Foundation Patient Registry. Pulmonary Fibrosis Foundation. 2017.

I think we're still going to continue to learn from this registry. There's an associated biorepository that we will be able to glean future biomarker results from, as well as other information that might become important in the subsequent care of patients with IPF.

PFF Patient Registry Conclusions

- A large number of patients with IPF and non-IPF are enrolling in the Registry and Biorepository.
- The diagnostic process for IPF and non-IPF is similar.
- Use of immunosuppression vs anti-fibrotic therapy differs dramatically between IPF and non-IPF.

PFF, Pulmonary Fibrosis Foundation; ILD, interstitial lung diseases.

Flaherty KR, et al. Pulmonary Fibrosis Foundation Patient Registry. Pulmonary Fibrosis Foundation. 2017.

I think it's very encouraging that there is a lot of interest now in IPF, and there are a lot of different drugs that are being developed. Various drugs are in phase 1, phase 2 development. Some drugs moving slowly towards phase 3. I'm not going to go through all of these on the list over here, but just to give folks an idea that there's a lot of activity in this disease area.

Latest Research on Emerging Therapies

Compound	Company	Structure/Route of Administration	Stage of Development	Mechanism of Action	Background Therapy	ClinicalTrials.gov Identifier:
PRM-151	Promedior/BMS	mAb/IV	Phase 2	Rh-pentraxin-2 protein	pirfenidone or nintedanib allowed	NCT02550873
SAR-156597	Sanofi	mAb/SC	Phase 2	Anti IL-4/IL-13	pirfenidone or nintedanib allowed	NCT02345070
FG-3019	Fibrogen	mAb/IV	Phase 2	Anti-CTGF	pirfenidone or nintedanib allowed only in the sub study	NCT01890265
STX-100/BG00011	Biogen	nAb/SC	Phase 2	Anti-integrin avB6	pirfenidone allowed	NCT01371305
PBI-4050	Prometric	Sm/oral	Phase 2	CTGF expression inhibitor	pirfenidone or nintedanib allowed	NCT02538536
TD139	Galecto/BMS	Sm/Inhalation	Phase 2	Galectin-3 inhibitor	Not allowed	NCT02257177

Sm, small molecule; mAb, monoclonal antibody; IV, intravenous; SC, subcutaneous; IL, interleukin; CTGF, connective tissue growth factor; BMS, Bristol-Meyers Squibb.

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
ClinicalTrials.gov

A lot of different companies are interested in new therapeutics for patients with IPF.

Latest Research on Emerging Therapies *(cont)*

Compound	Company	Structure/Route of Administration	Stage of Development	Mechanism of Action	Background Therapy	ClinicalTrials.gov Identifier:
MN-001 (tipelukast)	MediciNova	Sm/oral	Phase 2	Leukotriene receptor antagonist	nintedanib allowed	NCT02503657
KD025	Kadmon	Sm/oral	Phase 2	ROCK2 inhibitor	Not allowed	NCT02688647
CC-90001	Calgene	Sm/oral	Phase 2	JNK1 inhibitor	NA	NCT03142191
GLPG-1690	Galapagos	Sm/oral	Phase 2	Autotaxin inhibitor	NA	NCT02738801
Omipalisib	GSK	Sm/oral	Phase 2	P13K/mTOR	NA	NCT10725139
GBT440	Global Blood Therapeutics	Sm/oral	Phase 2	Hb O2 release stimulant	NA	NCT02846324

Sm, small molecule; mAb, monoclonal antibody; IV, intravenous; ROCK2, Rho-associated protein kinases; JNK, Jun N-terminal kinases; P13K, Phosphoinositide 3-kinases; mTOR, mammalian target of rapamycin; GSK, GlaxoSmithKline.

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As well as repackaging or repurposing some older drugs that might have a therapeutic role for IPF. Think about antibiotics, like cotrimoxazole, doxycycline; sildenafil has been around for a while. These are all still being studied in IPF.

Emerging Treatments *(cont)*

Compound	Company	Structure/Route of Administration	Stage of Development	Mechanism of Action	Background Therapy	ClinicalTrials.gov Identifier:
Inhaled Treprostinil	United Therapeutics	Sm/inhalation	Phase 3	Prostacyclin	NA	NCT00705133
Mesenchymal stem cells		Cells/IV	Phase 3	Regeneration of alveolar epithelium	NA	NCT02013700
Cotrimoxazole/ Doxycycline		Sm/oral	Phase 3	Antimicrobial	NA	NCT02759120
Sildenafil		Sm/oral	Phase 3	PDE5 inhibitor	NA	NCT00517933
Losartan		Sm/oral	Phase 3	ARB	NA	NCT00879879

Sm, small molecule; PDE5, phosphodiesterase type-5 inhibitor; ARB, Angiotensin II receptor blockers.

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So, the key take aways from this is that the prognosis of IPF remains unpredictable. It's very important that there be an early diagnosis and appropriate management put in place. This is vital to maintain patient's quality of life and slow disease progression. Disease management is crucial for patients with IPF and should be comprehensive to include the following: antifibrotic therapy, pulmonary rehabilitation, management of comorbidities, supplemental oxygen, if and when needed. Providing psychosocial support; lung transplant for select patients; and very importantly, once again, every patient with IPF should be given an opportunity to get enrolled in a clinical trial, so that future generations of patients who develop IPF, or future patients, can benefit from the patients of today. Because the patients of today are benefiting from patients 10 or 15 years ago who enrolled in the CAPACITY, ASCEND, and INPULSIS studies, that enabled the approval of the 2 currently available antifibrotic agents.

Key Takeaways

- Prognosis for IPF is unpredictable.
- An early diagnosis and appropriate management are vital to maintain quality of life and slow disease progression.
- Disease management is crucial for patients with IPF, and includes the following:
  - Antifibrotic therapy
  - Pulmonary rehabilitation
  - Managing comorbidities
  - Supplemental oxygen (if and when needed)
  - Social/psychological support
  - Lung transplant for select patients (early referral encouraged)
  - Clinical trial enrollment.

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