Clinical Cases in Interstitial Lung Disease

David Lederer, MD, and Imre Noth, MD

Overview: David Lederer, MD, and Imre Noth, MD, take a case-based approach to the management of patients with an interstitial lung disease (ILD). They discuss the evaluation and diagnosis of a patient with suspected ILD, including the role of the multidisciplinary team. Drs. Lederer and Noth review available treatment options, focusing on antifibrotic medications, lung transplantation, and pulmonary rehabilitation. Factors to consider in selecting evidence-based treatment are reviewed, including genetics, environment, and lifestyle. Key aspects to include in the assessment and treatment of an acute exacerbation are highlighted as is the importance of initiating palliative care early in the disease course.

Content Areas

- Acute exacerbations
- Comorbidities
- Epidemiology
- Evaluation and diagnosis
- Future Directions
- Idiopathic Pulmonary Fibrosis (IPF)
- Palliative care
- Pharmacologic treatment
- Pulmonary rehabilitation and lung transplantation

Cases

Target Audience

This activity is intended for pulmonologists, rheumatologists, and other clinicians who may encounter patients with ILD and/or connective tissue diseases.

Learning Objectives

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

- Diagnose interstitial lung diseases in a timely manner through optimal use of diagnostic criteria and radiologic findings
- Chart disease course during the management of ILDs
- Optimize treatment response in the management of ILDs with appropriate assessment and follow-up
- Develop evidence-based, individualized treatment plans for ILD management

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The estimated time to complete the activity is 1.5 hours.

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Editor's Note

This is a transcript of Dr. David Lederer and Dr. Imre Noth's presentation "Clinical Cases in Interstitial Lung Disease."

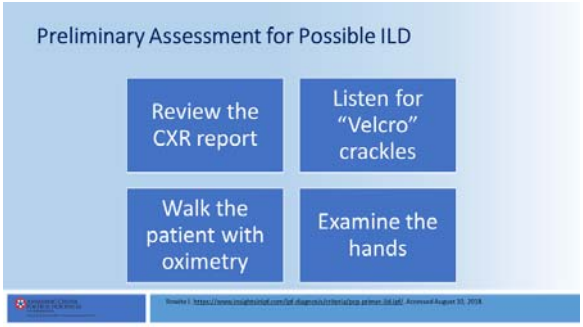
Symptoms suggestive of ILD

Jackie is a 62-year-old woman who presents to your clinic following several days of "the flu." She is referred to you by her primary care provider who is concerned about pulmonary infiltrates seen on her chest x-ray. She is complaining of persistent cough, shortness of breath, and dyspnea on exertion, going up 2 flights of stairs.

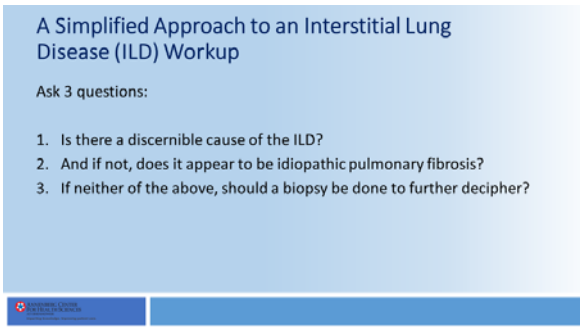
History:
Jackie reports that her exercise tolerance has been decreasing for some time. Her husband reports that her nightly dog walks have become progressively shorter over the past year. Her social history reveals that she is a former smoker. She has been a homemaker all of her married life. Her family has had pet birds in the house until recently.

Dr. Noth: Let's talk about preliminary assessment for possible interstitial lung disease. When we focus on the patient, we really take in several different aspects of what's going on, but there has to be a clinical suspicion, and usually that gets triggered by an abnormal chest x-ray, or computed tomography (CT) scan. We're going to put that in context with the patient's history and physical. Some key elements with regard to that physical are going to be the presence or absence of Velcro crackles. The crackles are pretty much universally present in patients with honeycomb pattern on their CT scan, which would be consistent with idiopathic pulmonary fibrosis.

We tend to take a look at other physical aspects, such as the hands, or rashes, or imploring symptomatology that might reveal an underlying connective tissue disorder. Then, I like to incorporate in addition to pulmonary function tests, 6-minute walk testing. The reason I do that is it's a wonderful functional assessment of the patient to see if there really is a ventilation/perfusion (V/Q) mismatch that results from whatever's going on in the lungs. That gives us some idea of what the state of the patient is.

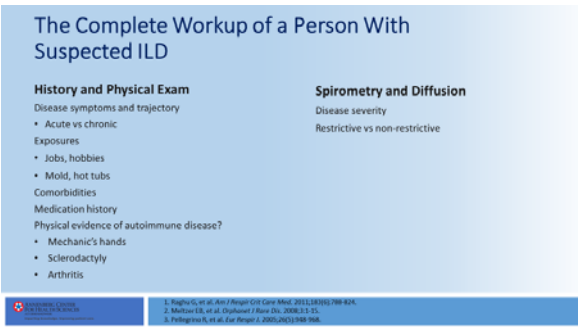


When we approach these patients, the simplified approach is really asking a few straightforward questions. Always looking to see if there's a cause. If there is no cause, does it appear to be idiopathic pulmonary fibrosis? Of course, if neither one of those fits, then would a biopsy provide additional information that would help simplify what we think this might be? That's important to recognize, as well, because it's true that sometimes you can get a biopsy result that isn't actually going to add information to the case. The reason for that is that the biopsy results can be pretty universal in a lot of different situations. It's important to remember that usual interstitial pneumonia is not definitive for interstitial pulmonary fibrosis (IPF) alone, and that we see that in other interstitial lung diseases as well.

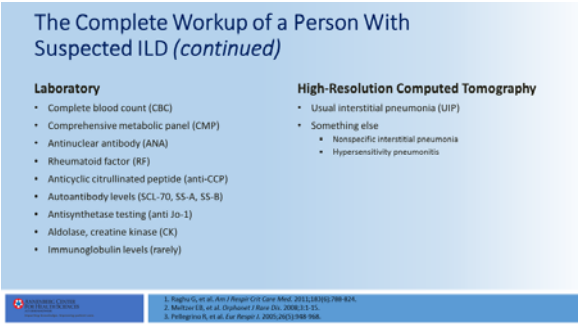


What are the things we consider in the workup in the patient with a suspected interstitial lung disease? Well, as we do that history and physical, we're trying to pick up on things that will tell us if it's acute vs chronic. We're looking at the exposure history the patient may have experienced. What hobbies they were engaged in. Whether they had mold exposure from hot tubs or moldy basements. We look to see what their comorbidities look like, what constellation might be there that really helps direct us in one direction or another. Their medication history, could there be a drug toxicity that would lead to the process.

Well, we then look for physical evidence of the autoimmune disease possibilities, as I kind of suggested earlier. Things like mechanic's hands, or sclerodactyly, signs of arthritis. The spirometry and pulmonary function tests are really going to give us some indication of disease severity. They're not going to really indicate to us which one of the interstitial lung diseases are there, on the whole. They really just tell us whether or not the process is restrictive or not.



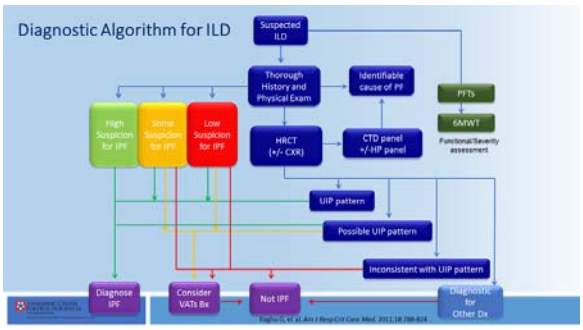
Now, the lab work can be very helpful, and the reason is that the serologic testing for many of the connective tissue disorders would really provide strong antibody support for what we might suspect is an underlying connective tissue disease. Now, the high-resolution CT scan is probably our most powerful tool, and the reason is if we pick up a pattern of honeycombing, it's going to be very consistent with usual interstitial pneumonia. As I mentioned already, usual interstitial pneumonia, while not unique to IPF, is what you're going to see on a biopsy when you have that honeycombing. It tells you that doing a biopsy isn't going to get you where you want to go. That's in contrast to when you've considered possibilities like nonspecific interstitial pneumonia (NSIP) or hypersensitivity pneumonitis (HP). Where in HP you might see granulomas, and NSIP will really show you this diffuse pattern that looks like the whole lung was hit at once.



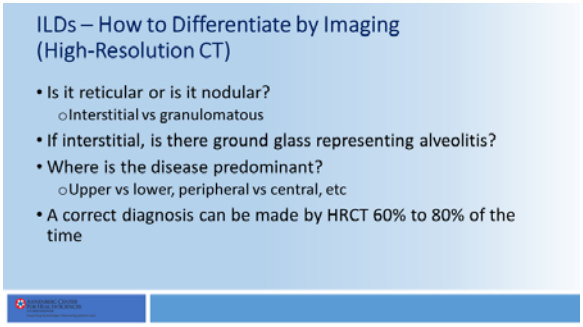
As I was just mentioning, the exposure history becomes very important. The reason for that is, we have to think of exposures as not just what's in the environment, but also drug toxicity. Drug-induced interstitial lung disease is a big category that we will often see. One of the great sites that I grew up with and continues to be an incredible resource is Pneumotox.com, which lists almost every last possibility known to man, as people put in new drugs as they evolve over time as having been associated with an underlying interstitial lung disease. I would really advocate that be used as a resource by clinicians when they see patients.

What is the diagnostic algorithm in these patients? Well, as I kind of suggested earlier, we have a suspected interstitial lung disease, the first step is a thorough history and physical. After that, the most powerful tool that we have is that high-resolution CT scan. In reality, it's going to give us a diagnosis 60% to 80% of the time. You couple that to getting the serologies, and that'll really help point you towards a connective tissue disorder, and a hypersensitivity pneumonitis standard panel (HP) panel will really help direct whether or not there are exposures to known molds and allergens that might lead down that particular path.

From there, we really decide whether or not there's a UIP pattern on that CT scan, and if we have a high clinical suspicion for IPF, the diagnosis is done. If it's a low clinical suspicion for IPF, that's where we start to work up other possibilities, where we think about a video-assisted thoracic surgery (VATS) biopsy so that we can get a read on the slide that might point in directions other than IPF. Of course, we can be led down that path by the high-resolution CT scan to begin with, if there's an inconsistent pattern, or if the pattern on the CT is suggestive of another diagnostic possibility.

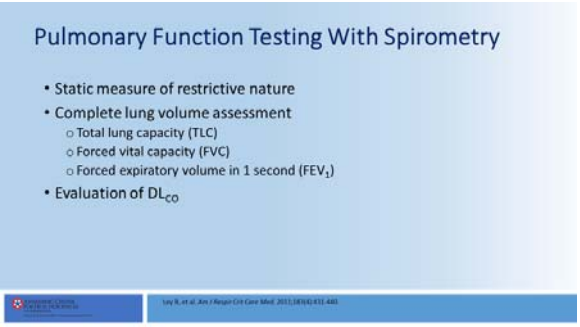


How can we use that imaging? It turns out the imagining is pattern recognition, of course. The first question that we ask is, is it reticular or is it nodular? I can tell you that in medical school I grew up with the term, reticular-nodular. Let me get that out of everybody's head. I try to break these down very disparately either into reticular or nodular because they tend to correlate with an interstitial pattern vs a granulomatous pattern. It's incredibly rare to see a true film that is both reticular and nodular. It'll predominantly be one or the other. Of course if it's interstitial, the next question is, is there ground glass representing an alveolitis? And then pattern recognition again, is it upper vs lower? Is it peripheral vs central? We put that all into context, and a good thoracic radiologist will be able to make a correct diagnosis 60% to 80% of the time.

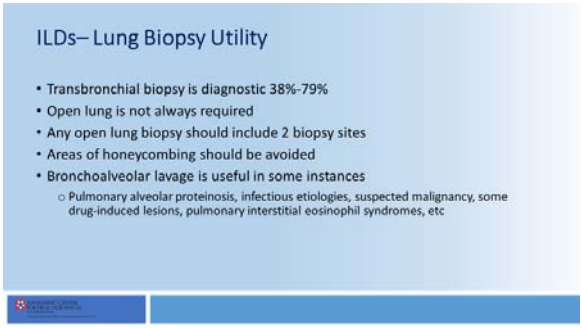


Well, pulmonary function testing is really a static measure of the level of restriction the patient is experiencing. Each part of it will give you a different piece of information. The total lung capacity really speaks to the total size of the lung. What that helps you realize is the level of restriction. The forced vital capacity is a flow, and that flow should have an increased elastic

recoil, and the air should be out faster. What we often see in these restrictive cases that are interstitial is a preserved airflow, whereby the FEV_1 will also be high, particularly relative to the FVC. The diffusing capacity of the lungs for carbon monoxide (DL_{CO}), it's important to recognize, really gives you a different piece of information. It's giving you what the capillary beds look like, and the alveolar destruction that you're seeing in this particular patient. Conversely, it could be a sign of underlying vascular disease, or simple anemia.

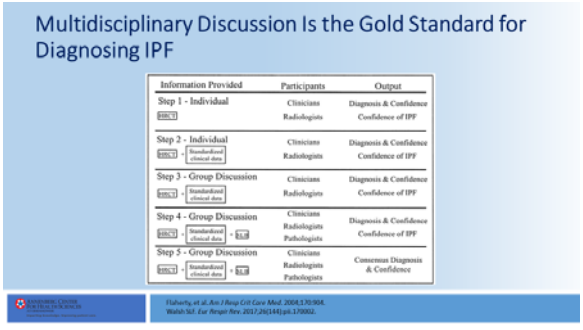


What's the utility of the lung biopsy? Well, again, it depends on what you're looking for. If you think the disease is a granulomatous process or is airway-centric, then that's where the biopsy with the instrument is going in the biopsy. The yield can be very high. In sarcoid for example, upwards of 90% to 95%. That's why we think of this as having a very diagnostic capability anywhere from 38% to 79%. Often, it'll mitigate the need for an open lung or VATS biopsy. Obviously, when you get a biopsy you want to avoid areas of burnt-out lung. Then the bronchoalveolar lavage (BAL) itself can be very useful for other possibilities, infectious possibilities, things like pulmonary alveolar proteinosis and pulmonary interstitial eosinophil (PIE) syndrome are easy to pick up on a BAL and help really guide the diagnosis.

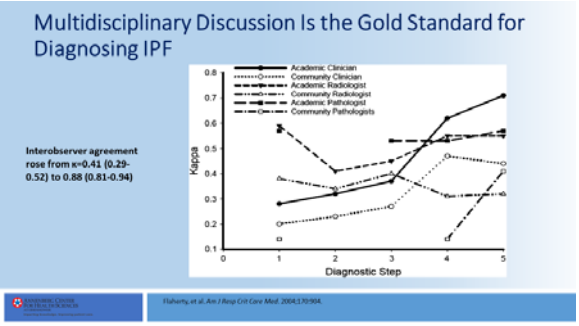


One of the most important concepts when we look at these patients in their interstitial lung disease categories is really recognizing that we do not at this juncture have a molecular definition for this disease process. Rather, a multidisciplinary approach, or agreements among the various disciplines as to what is going on, is currently the gold standard for diagnosing IPF, and frankly, many of the other interstitial lung diseases.

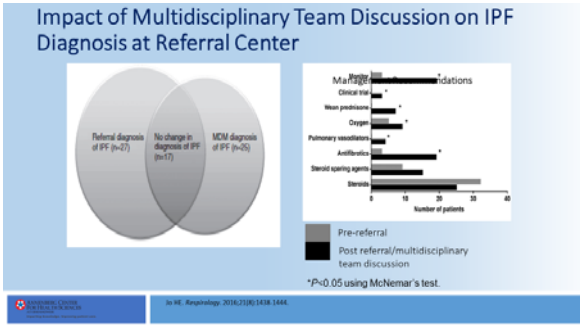
There was a terrific study done a few years ago where information was sent to clinicians in conjunction with radiologists and pathologists. They simply discussed the cases, both individually and then in concert, to really ascertain their level of agreement.



It's pretty amazing, because as you add information and you let people talk, the level of agreement really goes up. You see that that level of agreement is highest among the academic community who are really going to have the greatest exposure. I can tell you there've been 2 other publications since, but it basically said, the key is not that you're in an academic center, the key is that you see a high volume of these patients. Indeed, private practitioners who see large numbers of these patients have the exact same behavior as was in this study by Flaherty.



All right. What about the impact of the multidisciplinary team? Well, it turns out that team does a terrific job of not only reclassifying patients, but doing it in such a way that it really matters for the eventual treatment of these patients by changing management, and that's the goal. The goal is to be able to fit these patients into the correct box so that we know how to best treat them. When you send them to centers that do this multidisciplinary approach, they change a significant number of diagnoses, in conjunction with ultimately changing their treatment pattern, either by eliminating such things as steroid-sparing agents, or actually starting them, that they've decided it's not an IPF diagnosis.



In summary, as we think about the different considerations involved, we have to recognize that IPF is a diagnosis of exclusion. But the gold standard in today's world still relies on a multidisciplinary approach between the radiologists, the pathologists if you need the biopsy, and, of course, the clinical information. When you do this kind of exercise, you'll find that the clinician will sway the pathologist and the radiologist, depending on what the conditions are that the patient presented in. That's an important part of the exercise. Recognizing that the individual pieces of information, such as that UIP biopsy, out of context, have very limited value. When we put those altogether it gives us a much clearer idea of what the diagnosis is of the interstitial lung disease.

Key findings for IPF

Ralph is a 69-year-old white male seen by you 2 weeks ago with a complaint of 6 months of exertional dyspnea.

History:

- Former smoker with a 20 pack-year history
- Retired attorney
- Family history: grandfather died of lung cancer, but was a smoker
- Past medical history: coronary artery disease, diabetes mellitus, gastroesophageal reflux disease

Physical examination:

- Vital signs
  - Temperature: 98.4◦F
  - Heart rate 92 beats/minute
  - Blood pressure 163/90 mmHg
  - Respiratory rate 20 breaths/minute
  - O2 saturation on room air 92%
- Well-developed, well-nourished male in no apparent distress
- Mildly obese
- HEENT: unremarkable
- Heart: S1, S2, no murmurs/rubs/gallops
- Abdomen: positive bowel sounds, soft, not tender, not distended
- Extremities: clubbing, no cyanosis or edema
- Lungs: bibasilar rales

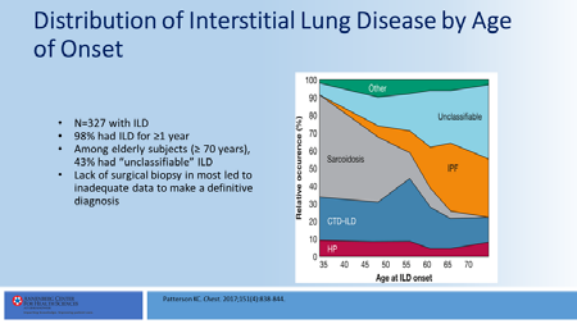
Further assessment of Ralph reveals:

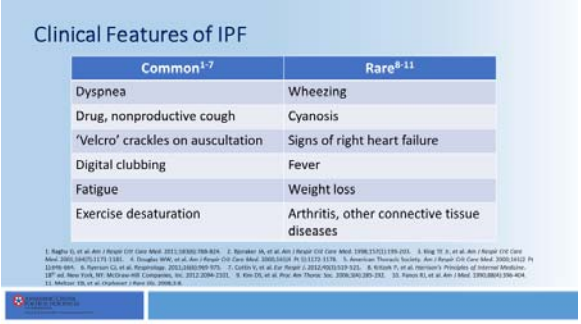
- No important exposures
- Dyspnea on exertion with 2 flights of stairs
- 6-minute walk test: O2 desaturation from 92% to 88%
- Pulmonary function test: FVC 72% predicted, FEV1/FVC ratio normal
- Chest x-ray: bilateral markings in the lung fields
- High-resolution CT: classic usual interstitial pneumonia pattern
- Serology: negative

A diagnosis of interstitial pulmonary fibrosis is confirmed. Treatment with antifibrotic therapy is initiated.

Dr. Noth: Let's talk a little bit about the distribution of interstitial lung diseases, and the reason that's so important is that when we think about patients and how to classify them, it's important to recognize that their age is a big factor. IPF is a disease of an aging community, and we know it's 3 times more likely in an 80-year-old than it is in a 50-year-old. That's in contrast to the connective tissue diseases which tend to afflict a younger grouping and, frankly, tends to be more female than male, unlike IPF which is more male than female.

What we can see is that we can see how that aggregates in these patients overall. The last example would be sarcoid, which again, presents in patients who tend to be a little bit younger. The reason is that they tend to burn out, so that by the time you see a 65-year-old sarcoid patient, it tends to be a much smaller grouping of those patients as they've had a chance to frankly correct themselves naturally over time.

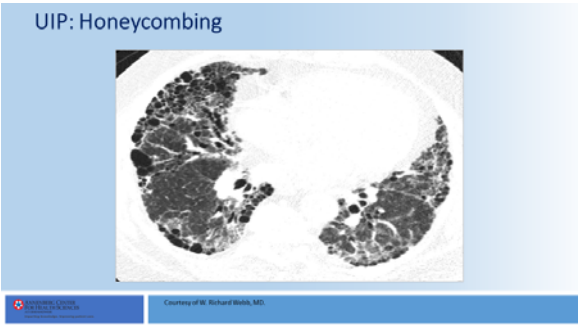




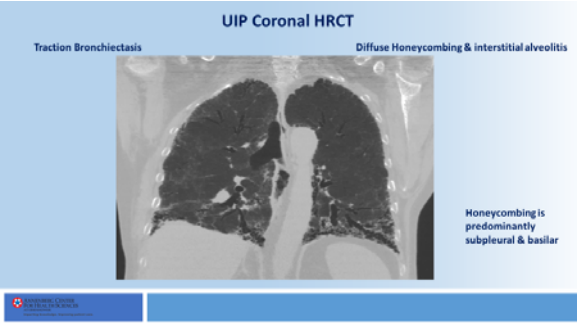
As we talk about IPF in specifics, while there are common overlapping presentations, there are elements that in constellation really help point to it. Certainly shortness of breath is a very generic symptom. But, when you couple that to a nonproductive cough and the Velcro crackles that are common in these patients, I would argue the Velcro crackles are in 100%. Digital clubbing tends to be in somewhere between 25% to 33%. Fatigue, of course, is incredibly generic. Exercise desaturation will be seen, depending on the level of severity. Things that should lead you in other directions are things like wheezing. While we may see some cyanosis, it's not a common presentation because that level of oxygen desaturation at a resting level is very uncommon.

We can see right heart failure in these patients, but it's often very late in the disease, so it's not going to be a common presenting element either. If we see things like fever, that should really make you think of another disease process. Now, weight loss and cachexia is something we're picking up more and more as these patients live longer and longer, because this was a grouping and an element of that cachexia that doesn't happen until very late. It's required that patients begin to survive before we see it. Of course, if you see arthritis or other elements of a connective tissue disorder, really you're talking about overlap or the interstitial pneumonitis with autoimmune feature category.

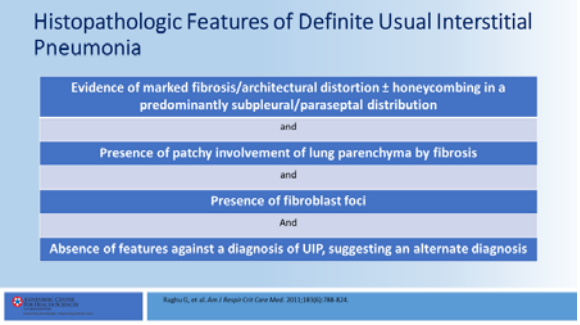
Now, the sine qua non amount of this disease, without a doubt, is the CT scan that shows you that honeycomb pattern. But it's important to recognize that honeycomb is only there about two-thirds of the time, maybe a little less than that. But it's important to recognize because it is definitive for that usual interstitial pneumonia pattern. We see exactly what the name describes. Cystic changes in the peripheral basal posterior elements of the lung that appear like a beehive's honeycomb. When you see that, if you biopsy, it will be a usual interstitial pneumonia pattern on the glass slide reviewed by the pathologist.



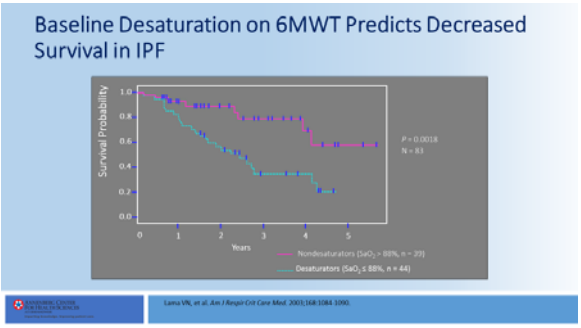
My favorite view of this is actually on the sagittal coronal sections, as opposed to the axials. The reason for that is you can really pick up that posterior basal presentation, mixed in with the bronchiectasis. The bronchiectasis is often difficult to separate on the axial's because you're cutting the tubes on-end. Whereas on this coronal section we really get this beautiful kind of sensation of the honeycomb down at the bottom.



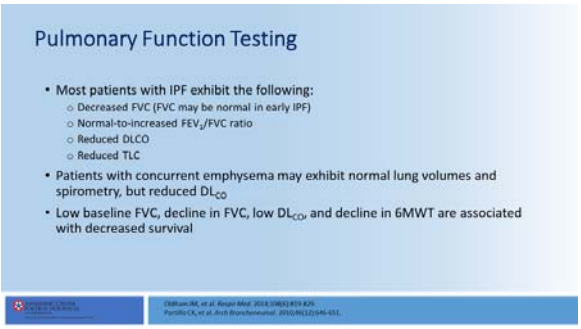
What are the histopathologic features that we see in a usual interstitial pneumonia pattern? The key feature is really microscopic honeycombing, much like we see on the CT scan, coupled to architectural distortion. We have presentation of patchy involvement of the lung. We should see normal lung, juxtaposed to abnormal lung. Fibroblastic foci have got to be there. That's one of the key elements. Then, because we are still a diagnosis of exclusion, the absence of features against an alternative diagnosis. We will often see elements of other processes, organizing pneumonia, the occasional granuloma. It's really about that overall impression. It's not looking for purity. It's looking for the overall sense of what that biopsy is representing in the lung as a whole.



Well, as we try to figure out how our patient is going to do, there are certain elements that really help. The dynamic integration of the 6-minute walk, which really tells you how bad the V/Q mismatch is going to be when the patient exerts themselves, is incredibly predictive of their mortality in a subsequent period. If they've shown signs of desaturation, that's a marker as a poor outcome.

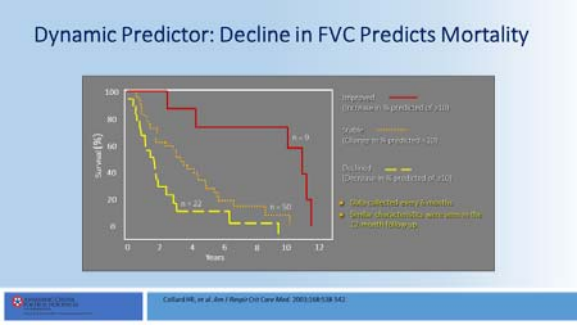


Pulmonary function testing in general helps designate these patients as mild, moderate, and severe. But that turns out to be a tough thing to use, and the reason is while we love to do that as human beings and put them into those categories, it doesn't tell us the rate. There's little doubt that a patient with a very severely reduced FVC is probably not going to do well. But the real question is, how long did it take them to get there? It's the same story with the DL_{CO} and total lung capacity (TLC). It's important to recognize that if you had concomitant emphysema that that's also going to reduce the DL_{CO}. You want to know how much of that DL_{CO}'s being reduced from a pulmonary fibrosis vs the emphysema.

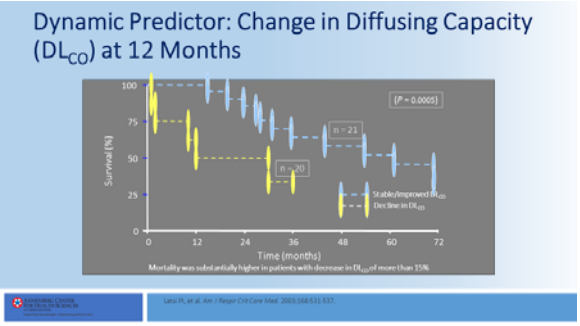


We know that these low-level baseline predictors all associate with poor outcomes, but when we move to dynamic predictors, dynamic predictors are really much stronger at predicting outcome. Why? Because they reflect

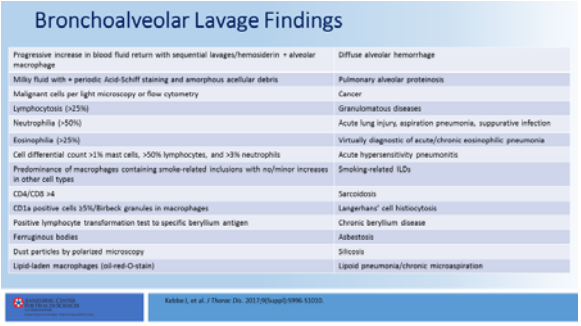
change over time. When you look at the decline in the FVC over a 6-month, or 12-month period, it's a terrific predictor of mortality, and this shouldn't surprise. There are numerous publications that really support this. What it's a terrible predictor of, is subsequent FVC decline, and isn't that fascinating? It doesn't help you separate out what the next behavior is going to be. Some of that really speaks to the heterogeneity of the behavior of the disease.



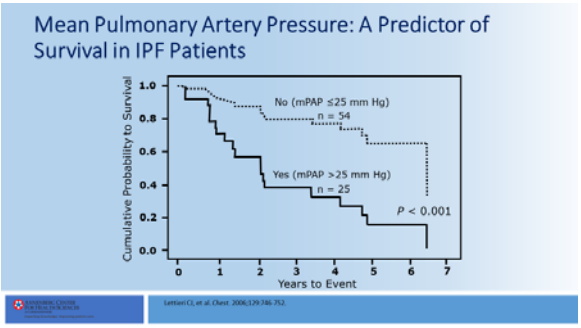
The same is true of the DL_{CO}. The DL_{CO} likewise, the dynamic decline in the DL_{CO}, really helps organize and predict what the behavior of the patient is going to be. If there's a decline in the DL_{CO} over the 6- or 12-month period, it's highly predictive of how the patient is going to behave.



The last kind of interesting element, that's had a growing body of evidence, would be the bronchoalveolar lavage findings. Really, that's got 2 aspects to it. The first is really recognizing that as a diagnosis of exclusion, it can show us things that can help us classify the type of patient that we have from an interstitial lung disease standpoint. That, of course, is going to correlate back to their prognosis. We can certainly discern whether or not there's diffuse alveolar hemorrhage, if there's a PIE syndrome, if there's sarcoidosis based on their CD4/CD8 balances, things of that nature can certainly come into play.



Lastly, pulmonary artery pressure. Well, it turns out that's really a sign and a reflection of that DL_{CO} and a sign if you will, of the level of severity of what's going on. When the pulmonary artery pressure starts to rise, that's a bad prognostic marker, because you're really starting to show that there are signs of right heart failure or cor pulmonale.



When we think about this in summary, we can clearly see that there are very clear features that'll help segregate and define our patient as IPF, and that we're then able to predict how they're going to do over time, based on their level of severity, but more importantly, how that severity changes over time. As we put that into constellation, we are better able to serve our patients by telling them how they're going to do by following them in our clinics and monitoring them over time.

IPF: acute deterioration

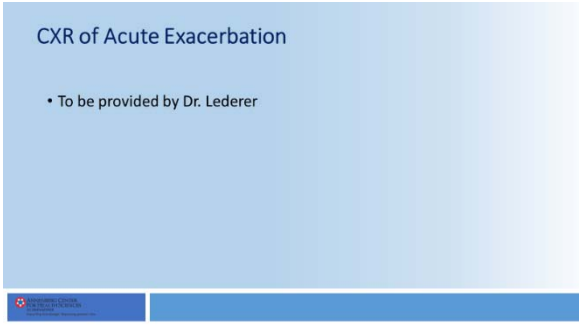
Phil is a 72-year-old man previously diagnosed with idiopathic pulmonary fibrosis who presents to the emergency department with 3 days of worsening dyspnea. He now has dyspnea at rest.

History:
He reports symptoms of an upper respiratory tract infection started 7 days ago. At baseline, he experiences dyspnea with stairs and hills. He normally uses O2 2 L/minute to sleep, but this has increased to O2 5 L/minute over the past 3 days.

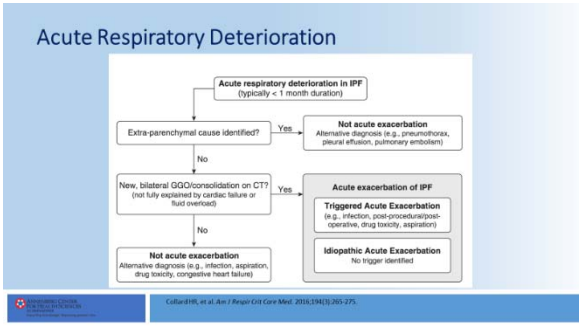
Physical examination:

- No fever, chills, sputum production, hemoptysis, chest pain or pressure, or leg swelling
- SpO2 87% on 10 L face mask → 92% on 15 L non-rebreather mask
- Vital signs
  - Temperature 97.2◦F
  - Heart rate 118 beats/minute
  - Blood pressure 140/72 mmHg
  - Respiratory rate 40 breaths/minute
- Visibly increased work of breathing with central cyanosis
- Difficult to assess jugular vein distention
- Diffuse crackles; no rhonchi or wheezing
- Tachycardic; S1 S2 regular; no murmurs or gallops
- No right ventricular heave
- No lower extremity edema
- Clubbing is present

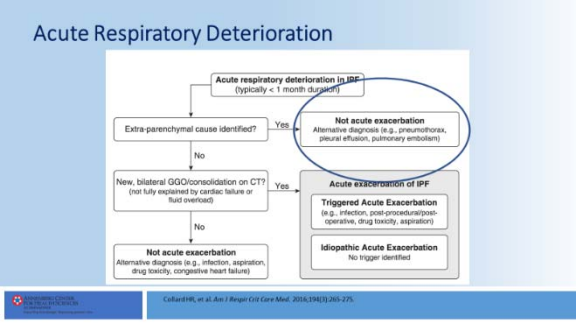
Dr. Lederer: Here we see an x-ray of a patient with acute exacerbation. We can see bilateral infiltrates that make us concerned for a variety of things on the differential diagnosis. We might consider pneumonia, heart failure, acute respiratory distress syndrome, aspiration, pulmonary hemorrhage, and, of course, in the old days, we would call an idiopathic worsening like this an acute exacerbation. But, the terminology's evolved, and I think it's important for us to think about this presentation in a broader way.



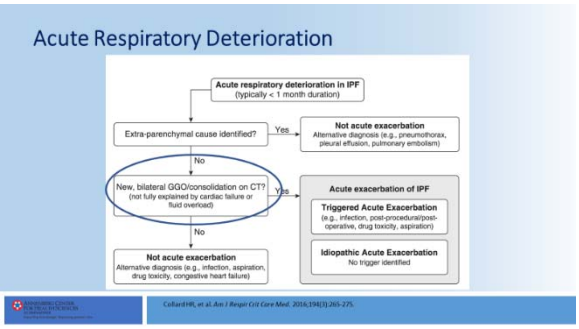
Just a few years ago, a group got together and decided to reclassify and use different terminology for acute exacerbations of IPF. We now call it "acute respiratory deterioration," and that's a broad category. That's an acute to subacute worsening in respiratory status, with increasing dyspnea, increasing oxygen requirements, much as you saw in the case. Of course, there's, as I mentioned, a broad differential for that acute respiratory deterioration.



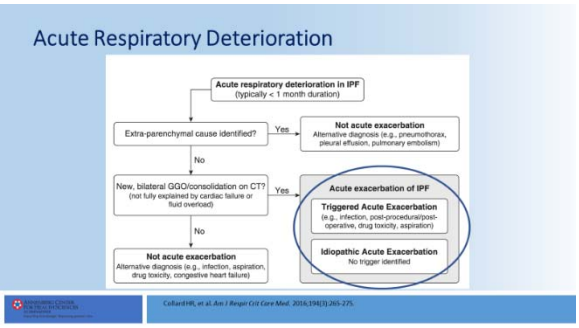
In some cases, it will be extraparenchymal in origin. It could be a pulmonary embolism. It could be a pleural effusion or a pneumothorax that's occurred. Of course, we'll do a workup to identify that. If that's the case, then we wouldn't call it an acute exacerbation.



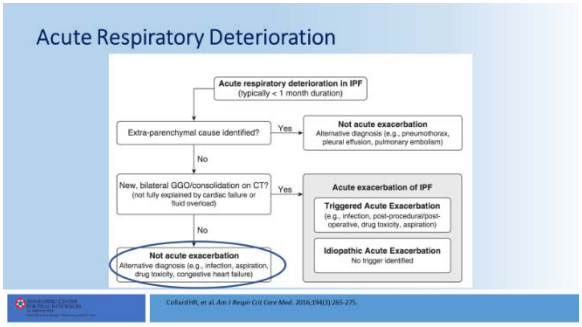
But, if there's no extraparenchymal cause identified, then we'll look at the lung fields on computed tomography (CT). If we see new bilateral ground glass opacities and/or consolidation, in that setting, if it's not otherwise fully explained by heart failure or infection, at that point, we are going to use the term "acute exacerbation of IPF" regardless of the cause. That's a new twist. In the past, acute exacerbation was always idiopathic.



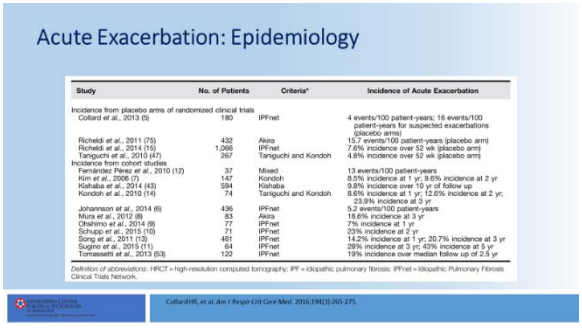
But, now, we split acute exacerbation into the old idiopathic category, but also now a new triggered acute exacerbation category. That trigger could be one of many things. It could be infection, it could be drug toxicity, aspiration. It could be post-procedural after a lung biopsy, for example.



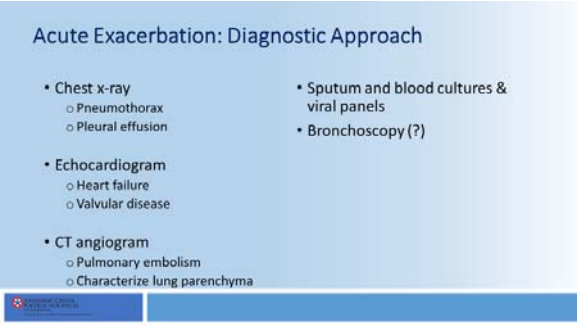
Now, on the other hand, if we don't see those characteristic changes on the CT scan, then, of course, it is something else. It's whatever we do see on the CT scan. It could be pneumonia and all those other things we mentioned before. So, the terminology is updated, and that's important to remember.



About 10% of patients with IPF, on average, will develop an acute exacerbation in a given year. That's a pretty high percentage. We don't understand why it happens. In the triggered sense, sure. Maybe it's infection. Maybe it's drug toxicity. Maybe it's aspiration. But, in a lot of idiopathic ones, where all the viral and bacterial studies are negative, it's not aspiration, and we're still trying to figure that out.



What are the immune pathways? What are the external exogenous triggers that might do that? What are the biological pathways inside the alveolar epithelial cells that are leading to that injury and then abnormal feeling afterwards, that's exacerbated in this setting? A lot to learn in that area.

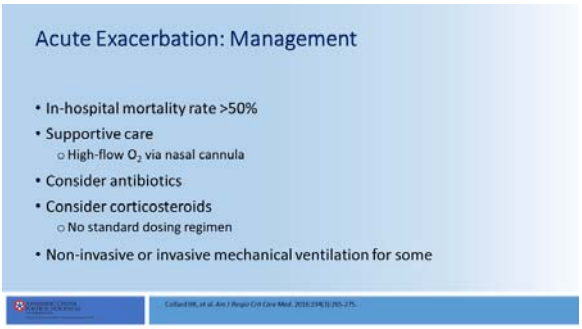


Clinically, it's important to think broadly about the differential diagnosis, as we talked about. An appropriate workup would certainly include a chest x-ray that might help identify extraparenchymal or parenchymal changes, pointing us towards a diagnosis. I think maybe not immediately, but fairly shortly after this patient presents, we'd want an echocardiogram to look at left ventricular (LV) function, valvular function, etc. And I recommend getting a CT angiogram of the chest to look for pulmonary embolism (PE), while at the same time being able to look for parenchymal disease, whether it's focal consolidation suggesting pneumonia or the bilateral ground glass consolidation suggesting an acute exacerbation. PE can occur with or without those bilateral findings, so the kind of classic acute exacerbation findings on CT. And, of course, the routine infectious workup is important.

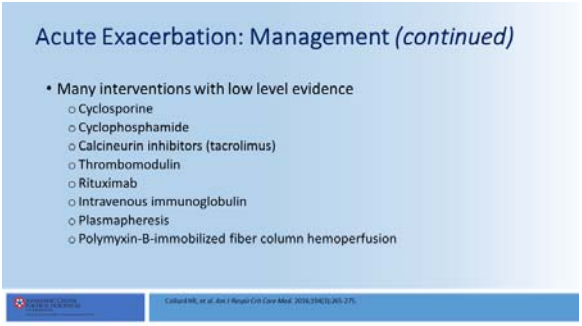
In the old guidelines for acute exacerbation, the recommendation was made to do bronchoscopy, but that's not feasible in most patients. None of us should feel pressured that we always have to do bronchoscopy. If it's in a clinical setting where you think it's safe, for example, if they're on a ventilator, and their fraction of inspired oxygen (FiO_2) and pressures are low enough, it's certainly reasonable to consider, but not necessary in all cases.

Let's shift to management. Management's challenging because there really are very few guidelines and there's no one standard of practice for this. I will say the mortality rate is quite high, over 50% in-hospital mortality, and even when you extend it out to 6 months or a year, it's much higher. This is not the same as your chronic obstructive pulmonary disease (COPD) exacerbation where they're often mild or moderate, and they tend to have better outcomes. Mostly supportive care, oxygen. I will say high-flow nasal cannula oxygen has really revolutionized the management of these patients, and there are patients who we can bridge to recovery, not frequently. Sometimes we bridge them to transplant, which can be a very important therapy.

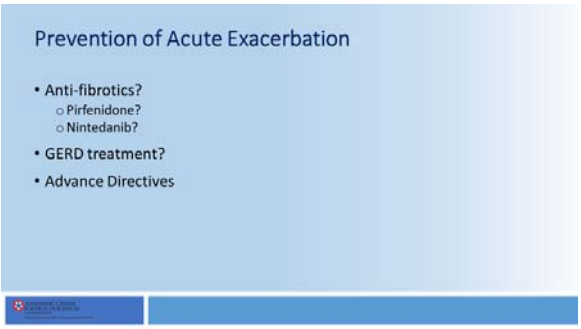
Antibiotics are often used. Corticosteroids. No clinical trials, ever, to document that corticosteroids are helpful in the acute inpatient setting and in acute exacerbation of IPF. I will say many centers do use corticosteroids. There's no standard dosing pattern. But, I do know that there are expert centers around the country that don't use corticosteroids in most cases. There's an American Thoracic Society (ATS) recommendation to avoid mechanical ventilation if possible. Certainly, having discussions in the office, long before the acute exacerbation occurs, about advanced directives and your patient's wishes and preferences is ideal, but it doesn't always happen. Sometimes those conversations will, of course, reverse when the patient is acutely ill and does want to be on a ventilator. That's, of course, quite challenging. Older patients who are quite sick, who end up on a ventilator have a very poor prognosis, so selecting the right patients for mechanical ventilation is important.



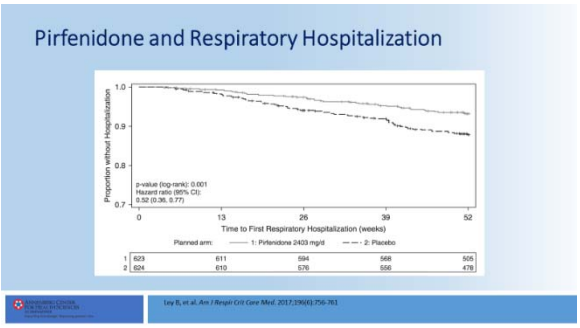
There are many publications, many other pharmacological agents and other therapies to treat acute exacerbations that have never been compared against a placebo. There's no controlled trials. These are case series drugs like cyclosporine, cyclophosphamide, tacrolimus, thrombomodulin, rituximab, and intravenous immunoglobulin (IVIG). People have used plasmapheresis, and even polymyxin B-immobilized fiber column hemoperfusion, mostly used in Asia, has been tried. Whether or not these things work, we don't know, and certainly shouldn't be used in all cases.



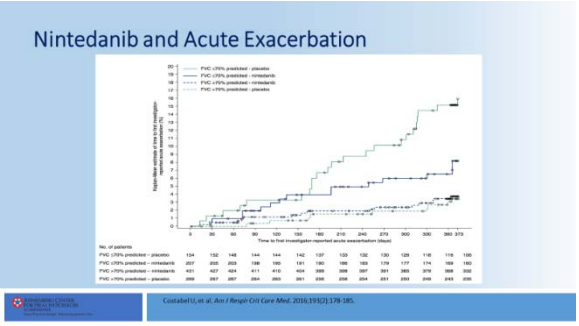
Finally, one of the exciting fronts in the past few years is that there are signals that we might be able to decrease the risk of acute exacerbation. The PANTHER-IPF trial suggested that immunosuppression might increase the risk of acute exacerbation, but we want to decrease the risk of acute exacerbation. If we look at published data that have come from high-quality randomized clinical trials of antifibrotics, including pirfenidone and nintedanib, we get interesting signals.



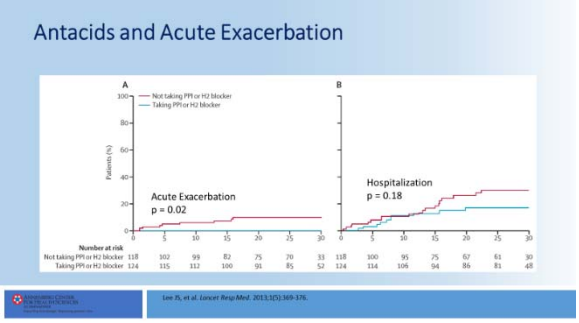
For pirfenidone, when we do randomized comparisons between treated and untreated, we see that pirfenidone reduces the risk of respiratory hospitalization over the course of 1 year. That's fairly convincing data. Those are randomized comparisons.



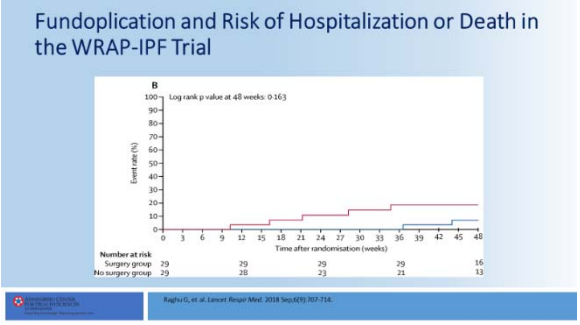
Very similar, nintedanib seems to reduce the risk of acute exacerbation in those with more moderate to severe disease. Really, I mean the people with an FVC of 50% to 70% predicted in a subgroup analysis of that study. Those with FVC values over 70% predicted, nintedanib did not seem to have an effect on acute exacerbation. I will say there are many post hoc and prespecified analyses looking at acute exacerbation with different signals, but this is encouraging and makes sense that it might prevent exacerbation in the sicker patients.



There's also data on antacids, that antacid therapy such as proton-pump inhibitors and H_2 blockers may reduce the risk of acute exacerbation. That data is really only observational in nature. There's never been, to my knowledge, a randomized trial comparing antacid therapy to placebo in IPF, but that is intriguing data.



There's also, in 2018, data on the role of surgical fundoplication, and this actually was a clinical trial, randomized trial, comparing surgical fundoplication to standard of care. The majority of people in both arms were on antacid therapy, and when we look at whether or not fundoplication could reduce the risk of hospitalization or death, we don't really see a significant signal. Numbers were small, and hospitalization was a secondary outcome. But, the jury is, I think, still out on whether or not fundoplication might have that kind of effect.



Just to sum things up, I find acute exacerbation to be one of the more challenging aspects of treating patients with IPF and other fibrotic lung diseases. We don't really have a standard approach. I think one of the really critical things, as I said, is to just look for alternative causes. If you can find something to treat, treat that. Then, if not, supportive care. In many cases, considering hospice care, or end-of-life care even in the ICU or step-down unit may be appropriate.

Palliative care

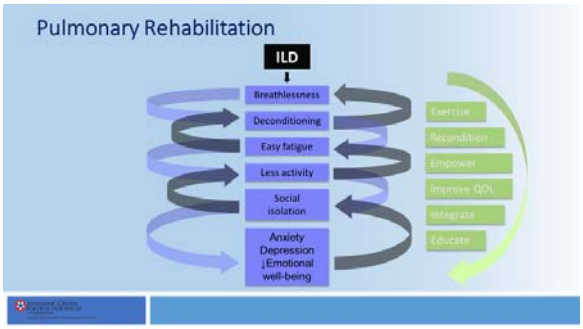
On his return visit, Ralph relays that he is greatly concerned about being a burden to his family. He wants to know if he should “get his affairs in order.” Evaluation reveals a Beck Depression Inventory score of 18, indicating mild depression.

Treatment plan:

- Continue antifibrotic therapy
- Begin home oxygen
- Refer for pulmonary rehabilitation
- Discuss other options, eg, lung transplantation
- Incorporate support groups
    - Primary caregivers
    - Primary care provider for additional regular visits to manage depression
- Continue monitoring lung function

Dr. Noth: As we start to think about the management of the patient, in general, we have to understand that we need to take the entire patient into context. We know that the rate of progression of these patients is very important. Probably the best thing that we've seen in the last few years is the availability of antifibrotic therapies. Their key effect is in slowing that rate of progression. Now what that does for us is, it really changes some of the paradigm in regards to our ability to predict how they're going to do, because we don't know yet. Those drugs are so new, we don't know yet how they change the Kaplan Meier curve of the data that we've had to date, in regards to their value. We know that there is basically a 50% reduction in the rate of decline. As we talk to them about their eventual outcomes, we incorporate that into the discussion. When we talk about palliative care to these patients, we're really focused on improving their quality of life, and making them understand what their longevity's going to be. When we tell them originally that they have a 50% 5-year mortality, that's based on data before we had treatments. Somebody who would go 1 year, now goes 2, potentially. Someone who would've gone 10, may go 20. The trap in that is when you're talking to an 80-year-old, ensuring 20 years is clearly a matter that's going to depend on numerous other factors. They have to take all of that into context. But our goal is to, as I tell them, isn't to make them live forever, it's to make them live better. That really goes hand in hand with the palliative care of the patient.

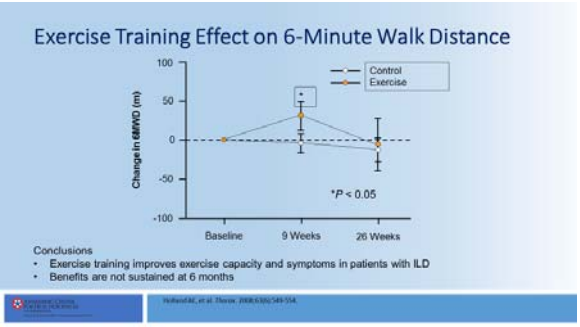
The good news is, is that this disease doesn't carry a whole lot of pain or discomfort. The result is that when we focus on the palliative care, it's really about making sure that their activities of daily living continue to be met to the best of our abilities. One of the strongest elements for that is pulmonary rehabilitation. Now, I often tease that pulmonary rehab is very much not dissimilar to my exercise program this morning. The more exercise I get, the more energy I have during the day, the more I was able to do, and the better I felt overall. It's really true for these patients as well, and there's been a growing body of evidence for that. As we think about it, what happens is, we help improve their breathlessness, their deconditioning, their sense of fatigue. That helps improve their social isolation, their anxiety and depression, and that really helps to empower and improve their overall quality of life.



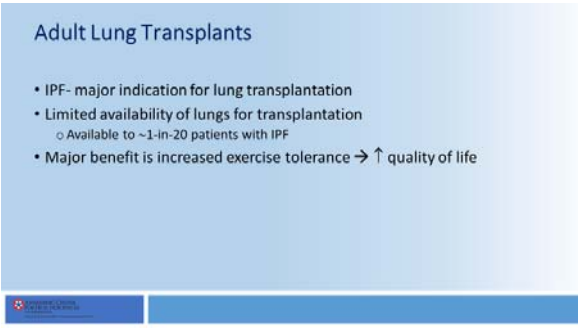
Realize that the rehab programs were originally designed for chronic obstructive pulmonary disease (COPD), so the irony is that they often come to me and tell me about their kazoo, because in COPD we use a kazoo to help them with purse-lip breathing, which has no impact on this disease whatsoever, because we've sent them to a COPD program. But, that's okay. It's really about the education and exercise, and the counseling and support that matters so much. These programs are often run by respiratory therapists and physical therapists. The idea, of course, is to teach them how to exercise themselves, with or without oxygen, depending on their needs, ultimately to improve their conditioning, to reduce their symptoms and

optimize their functional capacity, and as I pointed out before, increase their social participation.

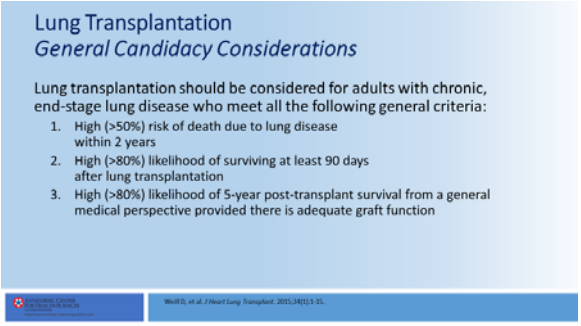
What's the evidence for that? There's very clear evidence that as long as they engage in the rehab, that they're going to have a training effect. They're going to improve their 6-minute walk distances. They're going to improve their exercise capacity. The heart and the lungs work together, and the more conditioned we get their hearts, the less demand it makes on the lungs to deliver more oxygen while they're exercising. That impact stays as long as they stay conditioned.



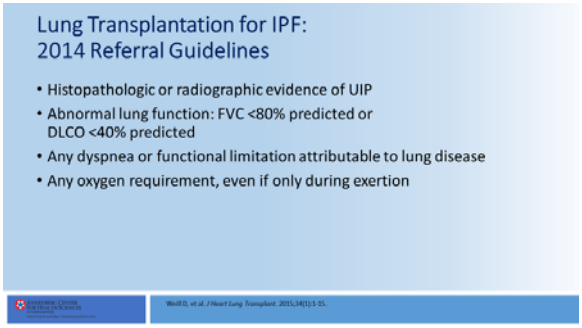
Well, what about transplants? Well, it's very interesting, that the truth of the matter is that IPF, after the lung allocation scoring system changed in 2005, moved to the top of the list, and became one of the major indications for lung transplant. In fact, patients have been doing better and better, but it's important to recognize that's merely 1 treatment. It's only going to be available to about 1 in 20 patients with IPF, given the number of lungs that are available, and that it tends to carry a 50%, 5-year mortality, also. What patients really get out of a lung transplant is a dramatic improvement in their lung capacity, and therefore their exercise tolerance. Their quality of life goes up. It's not to be taken lightly, but it is very, very important.



What's the candidacy for lung transplant? Well, the truth is it should be considered in every patient with IPF as early on as possible. As I just mentioned, we have a high risk of death within the first 2 years, and certainly within the first 90 days. That's our highest risk group. Overall, it still carries a pretty high mortality over the 5-year period because of graft rejection. Early on, the problems we see have to deal with acute rejection vs chronic rejection. But if we're going to be able to transplant these folks, we need to get them to the transplant centers, and to the transplant doctors, as early in their course as possible, so they can be in the best possible condition to undergo those transplants.



The current recommendations and guidelines as of 2014 included histopathologic or radiographic evidence of usual interstitial pneumonia, an FVC of less than 80%, really just documenting that they have a restrictive disease, with a DL_{CO} of 40%, and then any sense of shortness of breath or functional limitation. But the score really goes up as there's an increasing oxygen requirement. They purposely developed the score to weigh it in favor of patients with IPF who have increasing oxygen requirement, even if only during exertion.



What's the standard monitoring for these patients? I generally recommend that patients undergo pulmonary function test and a 6-minute walk test to elucidate their oxygen requirements every 3 to 6 months, with continued evaluation of their comorbidities. That's really one of the key ingredients here. On the one hand, we're monitoring their disease, we're trying to figure out if we're having some success using the antifibrotic, but the other is, the comorbidities matter. The more that we're able to pick those up and treat them, as appropriate, the better the patients are going to do. The high-resolution CT (HRCT), we do that really when there's clinical suspicion of worsening, looking for acute exacerbations, but more importantly looking for secondary processes that we can correct.

As we think about this in total, what are we really talking about here? We're really talking about how to manage the patient as a whole. Can we make them capable of doing more by empowering them with exercise programs? Can we focus on their comorbidities? Can we give them treatment options above and beyond the therapeutic agents that are out there, the pharmacological agents that are out there such as lung transplant, and oxygen, so that we can make their day-to-day lives better? As I said before, my objective is not necessarily to make them live forever, the objective is to make them live better. I think that this helps to do that.

Holistic care

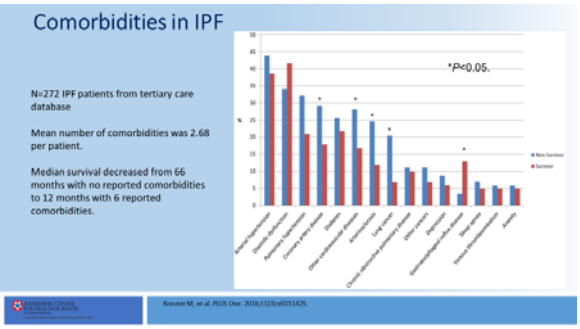
On Ralphs's next visit, repeat assessments show:

- Pulmonary function: moderate restriction with FVC further decreasing 7% and DLCO decreasing 12%
- 6-minute walk test: O2 desaturation from 92% to 86% but on 4 L O2

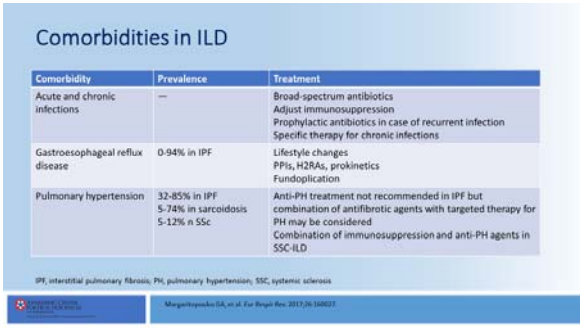
Evaluation now focuses on his comorbidities:

- Coronary artery disease
- Diabetes mellitus
- Gastroesophageal reflux disease
- Others

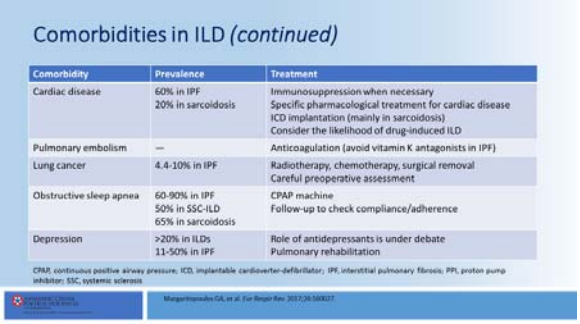
Dr. Noth: One of my favorite topics in the treatment of IPF is comorbidities. The reason is, while it's great to have new pharmacotherapies that help treat these patients, I continue to tout that I can do more for the patient by ensuring that we take care of their comorbidities than anything that's out there. That's not just true of IPF, that's true in a lot of different disease states. It's important to recognize that this is a systemic disorder. That while the primary impact is in the lungs, that we see arterial hypertension, diastolic dysfunction, pulmonary hypertension, that multi-vessel coronary disease, 4 times more common in an IPF patient than a non-IPF patient, 6 times more likely to get lung cancer, higher rates of depression, reflux disease is in 60% to 80% of these patients. These things matter.



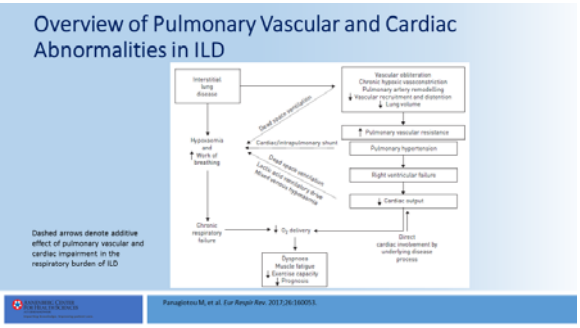
How do they matter? We know that if there are acute and chronic infections, we can treat those with broad-spectrum antibiotics. We can reduce immunosuppressant regimens for those that might have connective tissue disorders that are being treated. We can focus on specific therapies. Reflux, there's a growing body of evidence that the use of proton pump inhibitors in patients with documented reflux may have improved outcomes in retrospective data sets and most recently demonstrates the use of Nissen fundoplication bifurcation as a treatment option. Pulmonary hypertension tends to run pretty rampant in these patients, particularly at the end of the disease, particularly in IPF towards the very severe elements of the presentation. Whereas in things like sarcoidosis, we have a subgroup that will often have squeezing of the pulmonary vasculature as a result of a sarcoid, that may benefit from pH medications. And certainly, scleroderma has been treated for years with endothelial receptor antagonists, as an example.



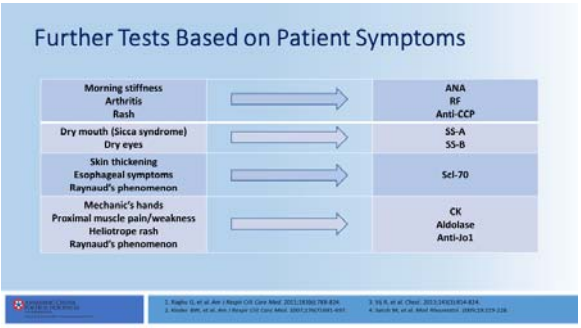
When we think about the cardiac disease, obviously we know there's a much higher prevalence, but sarcoidosis, as an example, can target the heart itself, and may require intervention by an electrophysiologist. We know there are higher rates of deep vein thromboses (DVTs) and pulmonary embolisms (PEs) in these patients, really demanding that they get treated with anticoagulation. How many times have I actually sent a patient to the thoracic surgeon to remove a lung cancer? They will die of their lung cancer before they die of their IPF, and so that's important to treat. We know there's concurrent sleep apnea. Now, a continuous positive airway pressure (CPAP) machine is a simple treatment. There's no reason not to treat depression in these patients, even if there is a justifiable cause for their depression, the role of antidepressants is clear.



When we think about the overview of the pulmonary vascular disease in these patients, it's not difficult to appreciate why this would happen. As the dead space increases and the V/Q mismatch worsens, that's going to put a strain on the heart. That's going to lead to more cor pulmonale, or right heart failure, forcing loss of cardiac output and loss of oxygen delivery, leading eventually to shortness of breath, muscle fatigue, loss of exercise capacity. We want to make sure that these things get treated as best we can, and we have lots of treatments for this particular aspect that's been observed in these patients.



What further testing should we engage in? Well, when we're diagnosing these patients, we're really trying to exclude other possibilities. I always tease that while the guidelines recommend an anti-nuclear antibody (ANA), erythrocyte sedimentation rate (ESR), and a rheumatoid factor (RF) when they first came out, they're growing in their point of view. Recognizing that a significant number of patients will have positive serologies for various connective tissue disorders, even without a positive ANA. Things like the rheumatoid factor and an anti-cyclic citrullinated peptide (anti-CCP) in patients who may be concerned with morning stiffness or a rash or an underlying diagnosis of possible rheumatoid arthritis. Dry eyes, dry mouth may indicate Sjogren's and warrant an anti-Sjogren's-syndrome-related antigen A (SS-A) and B (SS-B), whereas esophageal symptoms in Raynaud's may warrant an SCL-70. Likewise, for proximal muscle weakness or mechanic's hands, really demanding a creatine kinase (CK), or an anti-JO1 to pick up a polymyositis.



It's important to remember the psychosocial aspect as well, and realize this is pretty devastating for most patients to hear about this disease. We try to provide all of this care in collaboration in a multidisciplinary team, making sure that from a comorbidity standpoint, we've had a discussion with cardiology if appropriate, or with the gastroenterologist when Nissen fundoplication is necessary. That type of collaboration reassures the patient that they're getting the best possible care, including the psychiatrist, or psychologist if there's depression. And of course, the primary care doctor cannot be forgotten. They're the ones that are our gatekeepers. They're the ones that are going to see these elements first. Queuing them into what the possibilities are is very important for early intervention. That collaborative holistic approach really helps us mange the comorbidities, screen and manage for complications in the therapies, and their comorbidities, and help provide palliative care when appropriate.

As we summarize, to think about the comorbidities, it's clearly a dramatically important part of how we treat the patient. Every day we have new comorbidities that are being associated with both IPF and the interstitial lung diseases in general. They make a difference in both the day-to-day life of the patient, and their ultimate outcomes. The interrelationship to the disease progression is still being worked out. As we do, we come to realize that treating those elements affects the overall course of the patient.

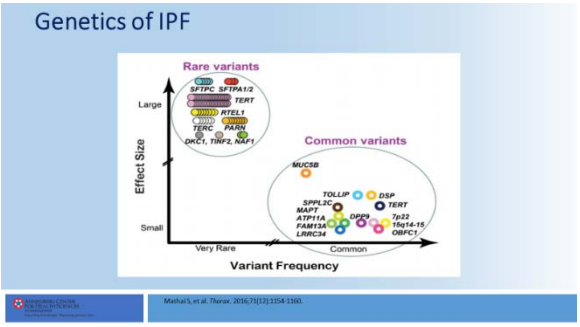
Genetics, environment and lifestyle

Omar is a 55-year-old man recently diagnosed with interstitial lung disease. He asks if he should undergo genetic testing. He has premature graying of his hair and thrombocytopenia. His father had idiopathic pulmonary fibrosis.

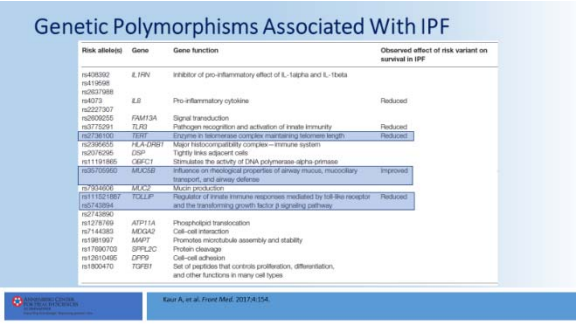
Dr. Lederer: The role of genetics in IPF has evolved quite a bit in this decade. We've learned a lot about many different genes from different studies, different study designs. These genetic findings have not yet made their way into the majority of clinical practice. I will talk about that when I give you a little bit of background on what we know about the genetics of IPF.

Some genes that have abnormal variants are associated with a very high risk of developing lung disease. These are very uncommon in the population. These are genes such as surfactant proteins A and C, TERC mutations, and TERT mutations, as well as RTEL1 and PARN mutations. All of those 4 genes are involved in telomere length, and we know that telomere shortening is associated with cellular senescence and aging, predisposing the lung to injury and abnormal healing.

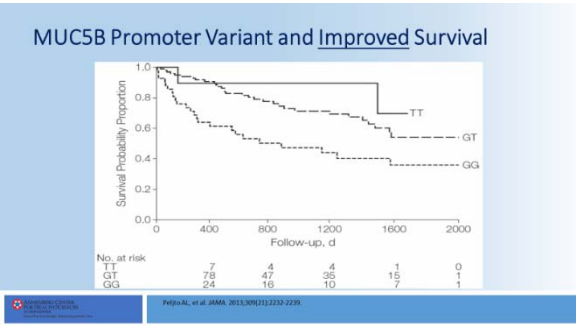
On the other hand, there are a whole lot of genes that are actually quite common, or fairly common, and associated with IPF risk. But, the penetrance is low, meaning that most people with that genetic variant will not develop IPF, fortunately. There are certain genes such as TOLLIP, DSP, a whole variety that have been found in genome-wide association studies that fall into that category. Then, in between those rare powerful and common weak genes, there's one called MUC5B, which is highly prevalent. It's about 30 plus, 30% to 40% of IPF patients will have a variant in the promoter single-nucleotide polymorphism (SNP) of MUC5B. But, also, 10% of unaffected people, 10% of the population, will also have this variant. So, quite prevalent, but less penetrant, and falling in between. If you have the variant, the risk can be high.



We've identified many, in the community, many, many genes associated with IPF risk, including genes involving interleukins, cell adhesion molecules, airway and host defense. As I mentioned, telomerase, genes responsible for maintaining telomerase length, and many others. Interestingly, some of these variants are also associated with increased mortality.

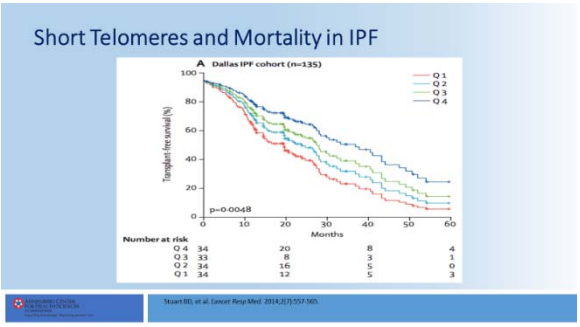


One of them, the MUC5B variant, actually, if you have the variant and you have IPF, you end up having better survival than those who don't have the variant. It's a little bit paradoxical. The variant increases the risk of IPF, but if you have IPF, the variant decreases your risk of dying, or at least your progression to death occurs more slowly. We certainly see that in people who are homozygous for the MUC5B minor allele, which is TT. But, the heterozygous GT genotype, much more prevalent and still better outcomes than the GG genotype.

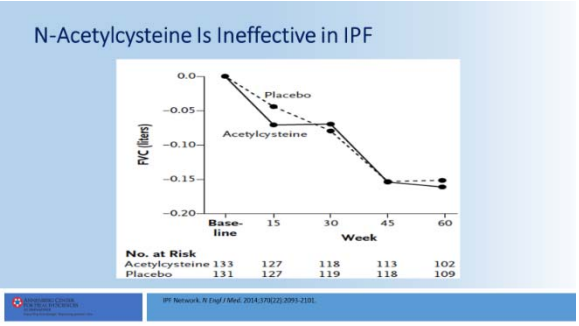


I mentioned short telomeres. These are important. Short telomeres can be detected in peripheral blood mononuclear cells. Not clinically, but in the research setting, and, of course, in alveolar epithelial cells and other lung cells. Shortened telomeres, sometimes related to mutations in those telomerase genes. Those short telomeres are associated with worse outcomes. I will say that, while we don't generally test for short telomeres or telomerase gene mutations in the clinical setting, when patients seem to be high risk, for example, as you saw in the case, someone with lung disease, family history, premature graying, thrombocytopenia, those things all point to short telomeres. That's what that case was about.

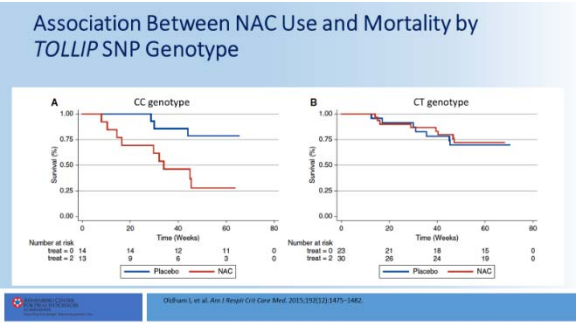
The lung transplant docs get concerned about telomerase mutations and get concerned about short telomeres because there's an increased risk of acute and chronic kidney disease and other complications, including bone marrow suppression, after transplant. So, clinically, some of the transplant docs are now asking for data on sequencing of some of these genes.



One very interesting, and this is like a glimpse of the future, I think, is a potential for what we call "precision medicine" in IPF. You may be familiar with the PANTHER-IPF trial, and specifically I want to focus on the N-acetylcysteine, or NAC, treatment arm compared to placebo. These were adults with IPF, FVC over 50% predicted, randomized to NAC or placebo over a year. That study, which was published a few years back now, showed really no effect of NAC on lung function decline, and really no consistent signal of a benefit.

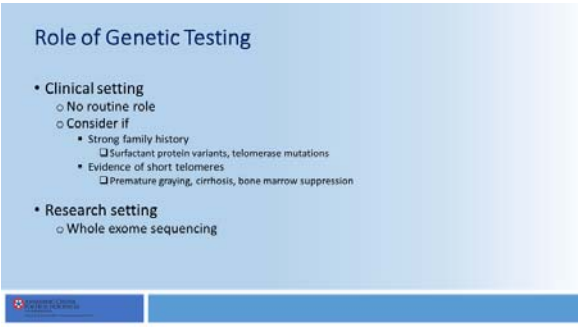


However, in a post hoc analysis, when some savvy investigators looked at this effect of NAC, not just on lung function but on survival, they found there's a variant in the TOLLIP gene. Variants in TOLLIP were associated with treatment effect, so that those who had CC genotype, even though there's only a few of these folks, people with the CC genotype actually had a survival benefit from NAC, whereas those with other genotypes, like the CT genotype, really NAC didn't seem to have an effect. This is a glimpse at whether or not we can use NAC, or in the future maybe other therapies, in people who we select based on their genotype. This needs to be confirmed in future studies, and I do hope there's another trial investigating this. But, this is very promising as potentially a role for NAC, although currently the recommendations are not to use NAC to treat IPF.



Clinically, let's talk about the clinical . . . the patient in front of you. Who gets genetic testing? My experience, and others have written about this as well, is that there is no role for routine genetic testing in patients with IPF. When a patient has a strong family history, or they have evidence of short telomeres, and these are the clinical features you saw in the case, premature graying, thrombocytopenia, sometimes cirrhosis even, family history of lung disease, those are settings where I will consider sending the patient, if they're interested, to a clinical geneticist and genetic counselor to see if genetic testing may be helpful. In most cases, in my experience, this doesn't change treatment, with that 1 exception of transplant. That is the short telomeres, or telomerase gene mutations. Transplant folks get a little nervous. But, in most cases, this isn't going to change my therapeutic approach.

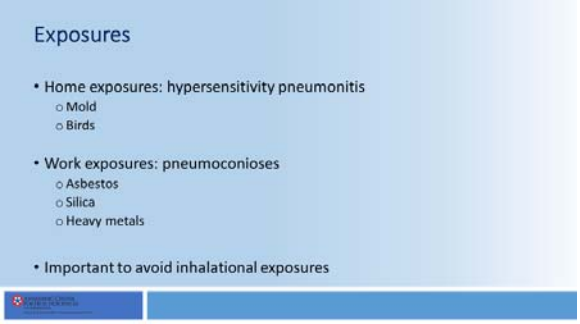
In the research setting, whole exome sequencing, whole genome sequencing, sequencing of whole families. There's a lot of exciting stuff in the pipeline, that's a few years from now.



I want to shift from genetics to talk about a couple of other factors related to ILD. These are things that, on the diagnostic front, on the management front, that are often glossed over a little bit. The environment that our patients live in is often a big factor in their lung disease. For example, if we've diagnosed a patient with hypersensitivity pneumonitis, then we know we have to remediate the mold, get rid of the bird. Or if we have a patient with a pneumoconiosis, like asbestosis or silicosis, usually they're

already out of the exposure, but, if not, we need to move them out of the exposure.

But, really, in a broad sense, we know that inhalational exposures are harmful and can cause lung fibrosis in susceptible patients, and hypersensitivity pneumonitis falls on a spectrum with, I think, IPF. We biopsy these folks, and we see all different patterns. So, for my patients with IPF, even if they don't have hypersensitivity pneumonitis, even if they don't have an occupational lung disease, I advise them to avoid inhalational exposures. Dusts, fumes, vapors, gasses, mold. I say anything you can smell. If you can smell paint fumes, get away. Not that we know that that works, but safety in the environment is important. I tell my patients, "Only breathe air."



Finally, I want to mention lifestyle and health maintenance. If you're a pulmonologist or pulmonary practitioner or nurse practitioner taking care of these patients, as you know, we always focus so much on the pulmonary aspects. Their primary care providers will focus on their other health care needs, but I think these things are really important. Smoking cessation, critical. I will say most patients I see with IPF, if they smoked, they quit long ago, but sometimes they're still smoking. Obviously critical. Talking to patients about travel, traveling with oxygen on an airplane, traveling on long car trips with oxygen, going on a cruise, traveling to where their destination is at altitude. There is guidance and literature, and even from the Pulmonary Fibrosis Foundation, on safe travel.

Exercise is important for patients with lung disease. If needed, we give them oxygen so that they can be as active as possible. Referral to pulmonary rehabilitation, really important intervention that can improve your patient's lifestyle and quality of life. Of course, achieving a healthy weight, particularly if they need to be referred for lung transplantation, and age-appropriate vaccination.

To sum that up, there's so many aspects of patient care that it gets complicated. The genetics is important to know, it's not yet really prime time in the clinical setting. I think we're on the verge, so it is important that you know this. And help your patients live a healthier and better life. Focus on their environment, their lifestyle, some of the choices they make, and help keep the safe with oxygen and exercise.

IPF therapy

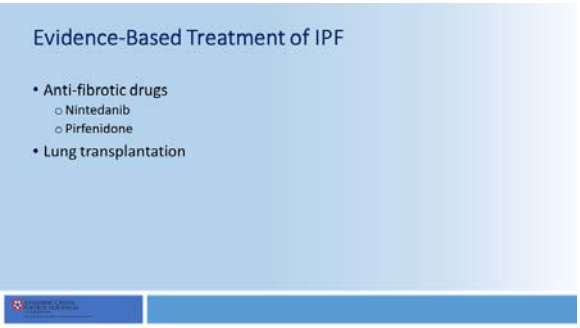
Ella is a 69-year-old woman who presented to your office 2 weeks ago with 6 months of exertional dyspnea. The history, physical examination, and serologic testing showed no identifiable cause of her dyspnea.

Diagnostic evaluation revealed:

- FVC 72% predicted with a normal FEV1/FVC ratio
- Chest x-ray exhibited bilateral markings in the lung fields
- Echocardiogram was normal
- High-resolution CT scan showed usual interstitial pneumonia pattern

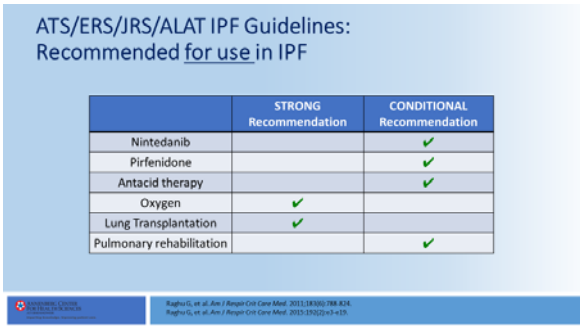
A diagnosis of interstitial pulmonary fibrosis was confirmed.

Dr. Lederer: Since we've made a diagnosis of IPF, we now should think about treatment strategies. I'm going to focus on pharmacological therapy, with nintedanib and pirfenidone. I'm going to talk about some guidelines, and I'm going to talk a little bit about lung transplantation.



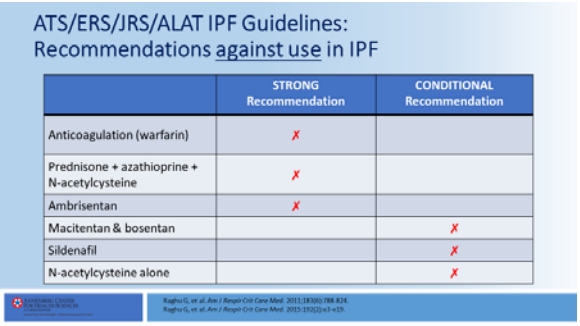
In 2011, and again in 2015, medical guidelines were issued for the treatment and management of IPF. These came from 4 medical societies - ATS, ERS, JRS, and ALAT. When we put the guidelines all together, we get some good information and help. The first thing is that strong recommendations have been made for the use of oxygen and lung transplantation in appropriate patients. Conditional recommendations have been made for the use of nintedanib, pirfenidone, antacid therapy, and pulmonary rehabilitation.

A quick note about a conditional recommendation. That doesn't mean it's a temporary or even weak recommendation. It ought to be interpreted as these are treatments that many patients will want, some patients will not want, and we need to engage in a shared decision-making process and work together with our patient to figure out what's best for them, as we do in most cases.



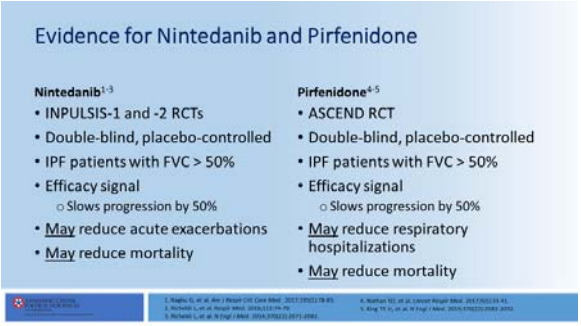
The guidelines also made recommendations against certain therapies, and this also really helps inform practice. For example, the guidelines made recommendations, strong recommendations, against the use of anticoagulation, specifically with warfarin. Triple therapy, which is prednisone, azathioprine combined with N-acetylcysteine, and ambrisentan, because of clinical trial data indicating harm. I will say that anticoagulation in that clinical trial was studied as a treatment for IPF, specifically compared to the placebo, with increased rates of mortality. However, if your patient has an indication for anticoagulation, such as venous thromboembolic disease or atrial fibrillation, please anticoagulate them as indicated. The

guidelines also made conditional recommendations against the use of macitentan, bosentan, sildenafil, and monotherapy with N-acetylcysteine.

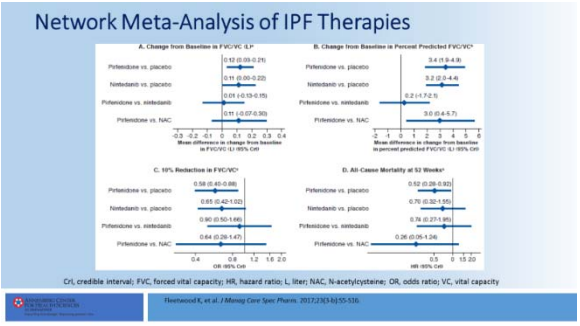


Let's focus now on 2 antifibrotics that are FDA approved for use in the United States to treat IPF. They are nintedanib and pirfenidone, and they share many similar qualities. They were both studied in double-blind, placebo-controlled, multinational clinical trials. Nintedanib was the INPULSIS-1 and -2 trials, pirfenidone in the ASCEND trial, and before that CAPACITY-1 and -2 trials. Both enrolled patients with IPF who had mild to moderate disease severity as indicated by a forced vital capacity greater than 50% predicted. Both drugs, each compared to placebo, showed similar efficacy signals, and that signal was a slow in the rate of progression by 50%.

So, unfortunately, that means that people aren't getting better, or even necessarily remaining stable for the rest of their lives. Even on treatment, people progress, however they progress more slowly, which can have a clinical impact. There are also signals that these drugs may reduce the risk of acute exacerbation or respiratory hospitalization, and even in meta-analyses, there may be trends and signals for it to reduce all-cause and treatment-related mortality.



In large network meta-analysis and in other pooled studies, we see these trends, that nintedanib and pirfenidone are both more effective than placebo at slowing FVC decline. We also see that, in the network meta-analysis, which is a fancy way of being able to compare 2 therapies that were never studied against each other, that there's not really a major difference in efficacy between pirfenidone and nintedanib, which makes sense because they both seem to have the same efficacy signal compared to placebo.



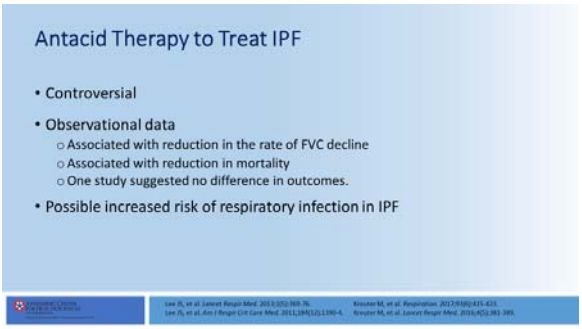
One of the major factors that comes up in clinical management, both during initiation of therapy and during maintenance therapy, are adverse effects of the drugs. Nintedanib commonly causes diarrhea. It is often manageable with loperamide, dose interruption, or lower dose. There is a lower dose available. Nausea, vomiting, less commonly, but can occur. There's also been some post-marketing reports of drug-induced liver injury, pancreatitis, thrombocytopenia, and a theoretical risk of gastrointestinal (GI) perforation since it impairs certain growth factor pathways.

Pirfenidone, on the other hand, doesn't have diarrhea as commonly, but does have upper GI side effects such as nausea, dyspepsia, loss of appetite, GERD symptoms, and can induce a photosensitivity skin reaction. So, for both medications, there's a fair bit of counseling that has to be done with the patient about how to take the medication. Pirfenidone needs a dose titration. Both medications absolutely have to be taken with food. Much better tolerated. Sometimes we need to add additional medications to help them tolerate medication. I will put everyone on an antacid if they're going on pirfenidone to prevent some of the upper GI side effects. Sometimes they'll need ondansetron or something else for nausea. As I said, loperamide for nintedanib.

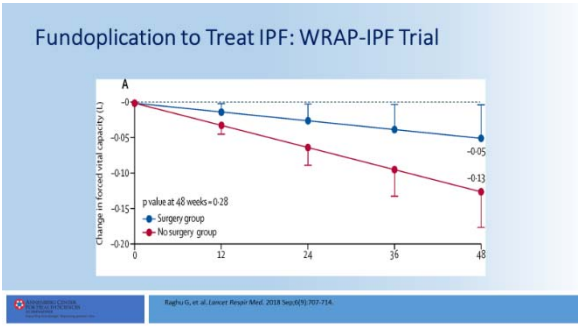
As I said, with initiation, talking to the patient upfront and deciding between one drug and the other is often all about side effects. Which set of side effects is more acceptable to your patient? There are also other factors. For example, with nintedanib, either avoid it completely or very closely monitor patients who are on full-dose anticoagulation or dual antiplatelet therapy because of a theoretical increase in bleeding risk. In addition, those at high cardiovascular risk, nintedanib may not be appropriate. There's a small signal of increased myocardial infarction in the INPULSIS studies for those taking nintedanib. Very small, but present.

Pirfenidone, on the other hand, doesn't necessarily have the same set of concerns, but a different set, and that's drug interactions. Pirfenidone should not be taken with fluvoxamine, an antidepressant, because it can raise pirfenidone levels. Similarly, high-dose ciprofloxacin, which of course is not commonly used, but that should be avoided in people taking pirfenidone. Then people who are currently smoking, the smoking will lower pirfenidone levels, and so in addition to, of course, smoking cessation efforts, pirfenidone may not be a great choice in people who are currently smoking.

There's also a little bit of controversy around the recommendation to use antacid therapy to treat IPF. This conditional recommendation is based not on randomized trial data, but on observational data, which is intriguing. There are nonrandomized comparisons between IPF patients taking antacid therapy and IPF patients not taking antacid therapy, showing that those who are taking antacid therapy have a slower decline in lung function. Even in 1 study, maybe even a reduced mortality rate. There's other data suggesting that that didn't occur in other cohorts, and there's even 1 study suggesting that antacids might increase the risk of respiratory infections in IPF. So, there's been some contradictory data, and some of that data follows those recommendations after the year 2015 when it came out.

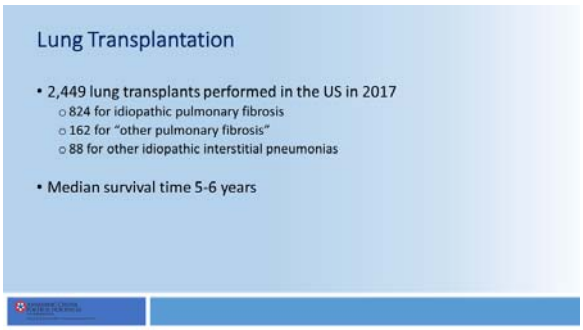


Now, in 2018, the WRAP-IPF study was published. This was a phase 2 trial of surgical fundoplication to treat patients with IPF who had objectively documented GERD as documented by a DeMeester score of over about 14. In this trial, those randomized for fundoplication had a nonstatistically significant reduction in the rate of decline in lung function over 48 weeks. Now, just to be clear, the lung function decline was slower on average, but not statistically significant. There were some secondary endpoints, time till decline in lung function or death, and others, that did show intriguing trends in the right direction. I think the jury is still out on whether or not aggressive treatment of reflux with surgical fundoplication is indicated. I guess we'll wait for the next set of treatment guidelines to help sort that out. Certainly, it's not something that should be used routinely in all patients.

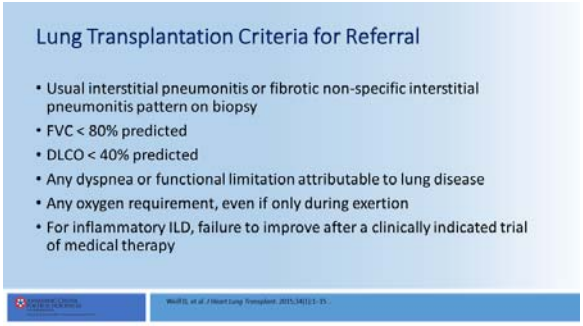


A couple of other things we do for our patients. Of course, supplemental oxygen certainly improves exercise capacity and improves acute dyspnea. This has been published, of course, in individual patients. We certainly see in some, but not all cases, that adequate use of supplemental oxygen in the home, outside the home, can relieve dyspnea. At least patients subjectively report less dyspnea. Pulmonary rehabilitation, as recommended by ATS, also very important. It can improve quality of life, improve exercise capacity. It may not have the same lasting effect as pulmonary rehab does for, say, a patient with COPD, but it still can have a positive impact on their lives. I prescribe pulmonary rehab to patients if they need any oxygen. So, if they need 2 liters when they're exercising, or 2 liters when they're walking, I will send them to pulmonary rehab at that point, if they're agreeable.

Then, I want to just have a word about lung transplantation. This is an excellent treatment for highly selected patients with IPF. There are not a lot of lung transplants performed. In 2017, there were just under 2500 lung transplants performed in the United States, and maybe just shy of 1000 of those were for people with interstitial lung disease. There's not enough lungs to go around, so we highly select these patients. If your patient is fit, physically fit, has very advanced lung disease, a lung transplant may be able to save their life or to prolong their life by years. The median survival time is 5 to 6 years. For older folks, older than 65 or 70, it's not going to be quite that long on average, but may still be beneficial in selected candidates.



The International Society for Heart and Lung Transplantation has issued guidelines on the timing of referral for lung transplantation. The bottom line is, if your patient has fibrosis, you should refer them for transplant. That may mean you're referring people early in the course of disease. That's okay. It's never too early to refer. They get to meet the transplant program, learn about it, get accustomed to it. As their disease progresses, they will then undergo additional testing, including invasive testing, and see if they're a candidate for lung transplantation. Don't wait til they're on 12 liters of oxygen. Don't wait til they're in the hospital with an acute exacerbation. Try to send them much earlier than that. Anyone with reduced lung function, anyone who needs oxygen, anyone with IPF, anyone with established fibrotic lung disease that is going to progress should be referred for transplant, again, at the time of diagnosis or shortly thereafter.



That's a lot of information about treatment. I do refer you to the ATS guidelines on treatment of IPF, published in 2011 and then updated in 2015. Wealth of information there. There's also the prescribing information for nintedanib and pirfenidone, which again is indicated for the treatment of IPF.

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