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Challenging Cases in PAH: A Deeper Dive

Dr. Mclaughlin:
Well, thank you so much. I'm really thrilled to be here today for this program, Pulmonary Arterial Hypertension: A Deeper Dive. I'm excited to touch upon a couple of topics that we don't speak about quite as frequently. I'm a Professor of Medicine **(inaudible…skip in audio)*0:16** Michigan, and I direct the Pulmonary Hypertension Program here, and I am thrilled to be joined by my good friend and colleague, Dr. Richard Channick, who also directs the Pulmonary Vascular Disease Program at UCLA. So, Rich, from cold, snowy Michigan to warm, sunny LA, welcome.

Dr. Channick:
Pleasure to be here, Val.

Dr. Mclaughlin:
So, as was mentioned, please feel free to send in your questions during the course of this talk. I think one of the most fun parts of programs like this for me is the question and answer period at the end, and Dr. Channick and I will do everything we can to try to get all of your questions answered either as we go along or at the end.

The learning objectives for this program are to discuss the 2018 World Symposium on Pulmonary Hypertension, new thresholds for the normal range of pulmonary artery pressures that we now use in the diagnosis. We'll talk a little bit about the diagnostic tests, functional classification and differential diagnostic considerations that we need to address to provide a diagnosis of pulmonary arterial hypertension and to develop treatment strategies for optimal management of patients, and we'll have a couple of cases, including one case of a very advanced patient that I think will provide some important teaching opportunities that we sometimes don't focus on.

So, in section 1 we'll talk a little bit about definition, diagnosis, and some of the management options. So this is the change in the hemodynamic criteria that was a result of the 6th World Symposium on Pulmonary Hypertension. Basically, the recommendation was to lower the definition from a mean pulmonary artery pressure of 25 to a mean pulmonary artery pressure of 20. On the left you see the old definition, and on the right you see the new definition that includes that mean pulmonary artery pressure of greater than or equal to 20. Of course, you still have to have a normal left heart filling pressure, a wedge of less than or equal to 15, and the pulmonary vascular resistance needs to be elevated.

Now, one of the reasons this was done is because of really a review of a lot of data suggesting that a normal mean pulmonary artery pressure is about 14 with a standard deviation of about 3, so really, the upper limit of normal that should encompass more than 95% of the normal population is a mean less than 20. I think that coupled with some more recent data about the worst outcomes in patients who have mean pulmonary artery pressures in that low 20 range, that 21 to 25 range, really is what spurred this change in the definition.

Now, there were some very modest changes in the classification as well. We all know that group 1 pulmonary arterial hypertension is that hemodynamic definition that I just spoke about without other significant heart disease, lung disease or thromboembolic disease, so the group 1 that we refer to as PAH that has the proteotype of idiopathic pulmonary arterial hypertension, what we used to call primary pulmonary hypertension. 1.2, inheritable PAH, and there have been a number of genes that have been identified that are associated with heritable PAH. There's drug- and toxin-induced. There's the associated connective tissue disease being the most common. 1.5

was added. This is something new in this classification, those very unique patients who, over the long-term, respond to just calcium channel blockers. They are those patients that have that very robust vasodilator response when tested with an acute vasodilator in the cardiac catheterization laboratory at the time of their diagnosis and then do well clinically on calcium channel blockers, so that is an addition or a change for this criteria for this classification at the 6th World Symposium, and then incorporating the PVOD and PCH subtypes into 1.6. So those are the main changes in group 1.

Group 2, pulmonary hypertension, anything that elevates left heart filling pressures can cause a more passive pulmonary hypertension, and you see many of the causes listed there: systolic dysfunction, diastolic dysfunction, valvular heart disease. Anything that results in hypoxemia can contribute to group 3 pulmonary hypertension. Group 4, chronic thromboembolic pulmonary hypertension is a very unique type of pulmonary hypertension that can sometimes be cured with a surgical approach. And then group 5 are patients with unclear or multifactorial mechanisms, and it's really a potpourri of different diagnoses there.

Now, the functional classification is very similar to the New York Heart Association Functional Classification. Class I is easy. The patient can really do whatever they want without getting short of breath. Class IV is easy. The patient can't do anything without getting short of breath or short of breath at rest or with even any minor exertion, or they have syncope. And II and III are a little bit in between those two. Functional Class II is a patient who can do ordinary physical activity without getting short of breath—or before getting short of breath, and Class III is less than ordinary. I often use a flight of stairs as a range between that. I would call a Functional Class II patient is someone who can go up a flight of stairs without dyspnea but might get dyspneic with a second flight of stairs, and the Functional Class III patient might not be able to go up a flight of stairs. Now, those Functional Class IV patients, those really sick patients, are few and far between, but sometimes we do get them, and they can be quite challenging, so I'll let Rich talk about a case that might be very demonstrative for that.

Dr. Channick:
Thanks, Val. Welcome, everybody. Yeah, we thought we would present this case that's, I think, **(inaudible)*6:54** what many of us face for some of our sickest patients—in other words, when they come into the ICU and some of the critical care aspects. I think one of the, really, advantages of having effective therapy for PH is that patients are living longer, but sometimes they get sicker, and I just thought I would go through a case that illustrates that and get a lot of Val's thoughts on how she manages these patients in the ICU.

So this is a 56-year-old woman with connective tissue disease, had been diagnosed with PH four years prior, and actually had been treated with combination therapy with an ERA and a PDE-5 inhibitor but doing reasonably well but noted over a couple weeks that she started getting worse—leg swelling, shortness of breath. She did admit to some indiscretion with dietary intake of salt, and she hadn't really been weighing herself regularly, which we certainly encourage all our patients to do. She also had noted maybe a cough and some nasal symptoms about a week prior to admission that she thought was just a URI.

On the day of admission, she actually had presyncope going up the stairs. She thought she was going to pass out, sat down on the stairs, and then was brought to the hospital. When she got to the hospital, she was awake but clearly mildly tachypneic, blood pressure was a little bit low, as you can see here, and she was mildly tachycardic with O_2 saturation on 2 liters 92%, wasn't normally on oxygen, and we could hear a pretty obvious right-sided S3 and a TR murmur along with clear peripheral edema. We got a quick echocardiogram, which confirmed a very poor-looking RV, severe pulmonary hypertension and what looked like a moderate pericardial effusion, which she hadn't had previously. She had maybe a small infiltrate in the left lower lobe but otherwise clear, and so she was admitted to the ICU for right ventricular failure.

What I'm going to do, and then again I'll get Val's thoughts—I mean, this is obviously a sick patient that we face—is how I approach these patients and what I call sort of the pillars of managing RV failure in the ICU, from assessing the severity, identifying and treating triggers, optimizing fluid status, i.e. preload, arterial pressure, inotrope and afterload reduction in RV. These are all things I think are important when we're managing these patients.

Val, maybe I'll stop and say, what do you think of a case like this? What's your sort of initial assessment and sort of initial thoughts?

Dr. Mclaughlin:
Yeah, I mean, I think, Rich, this is obviously a very sick lady. We're worried about her. I really love the way you've divided this up into the pillars of management, and I think it provides a really wonderful framework to go through such a sick case, so I approach it very, very similarly to what you've done here.

Dr. Channick:
Right, yeah. Great minds think alike, eh? Yeah, so this is... Everybody knows this, what are the parameters we look at for heart failure and cardiogenic shock and all the biomarkers that we look at and track, like lactate and BNP, and liver chemistries, renal function, are all things that obviously we try to do to assess severity. When we talk about triggers of right ventricular failure, I think it's another important

point, and these are the things that I always think about as why a patient has really sort of fallen off a cliff and why they deteriorated. I highlight or bold PE and infection, maybe with a special emphasis on infection because that seems to be often the trigger that pushes people over, but we've certainly seen hyperthyroidism that wasn't suspected, anemia. Obviously, noncompliance with medication or diet can do it. Anything to add to this list, Val, things you think about for triggers?

Dr. Mclaughlin:
Yeah, I think it's a great list. I think I would focus, in addition to what you highlighted, on just the volume management, and sometimes these folks can be fluid overloaded without diuretic withdrawal or interruption, like maybe they have one really high-salt day and they start retaining fluid, and then even though they are taking their diuretics, they are not absorbing them, and it starts that vicious cycle of volume overload, so I think that's really an important point to highlight as well as the others that you so nicely elucidated.

Dr. Channick:
Yes, it's really scary how little change in their sodium intake can really push them over the edge. So, when it comes to that, my first mantra is preload, preload, preload, and I think—and this is sort of editorializing in some ways—that what I learned over the years is that when people are taught that RV is preload-dependent and you can underfill the RV in these patients, that's very rarely the case. All these patients actually have excessive preload, and so I think I become more and more aggressive and impressed with the impact of really aggressive diuresis in patients. You look at these hearts. We all talk about ventricular interdependence and the fact that an overloaded RV can have an LV function. Would you concur with that, Val, that sort of general philosophy?

Dr. Mclaughlin:
Yeah, absolutely, Rich. I mean, every July I have to give this lecture to the house staff, right? because a sick PH patient comes in hypotensive. And what's usually the knee-jerk response to hypotension? It's give fluid. And in reality that's the right thing to do in such a small minority of PAH patients that come in in shock, in RV failure. I don't want to say you never do it because there is that occasional patient who's had a GI bleed or bad diarrhea or distributive shock. That happens occasionally, but more often than not these folks are volume-overloaded as it is, and if their neck veins are at 15 cm, 18 cm, there's no good in giving them more fluid. All giving them more fluid does is sit in the right ventricle and then worsen those problems that Dr. Channick was mentioning, the intraventricular interaction, and sometimes even cause worsening right ventricular ischemia, so it's really important. It's scary to people, but very often you need to push diuretics in these situations.

Dr. Channick:
Yeah, 100% agree. My mantra again to the house staff is, whatever diuretic dose you think you're going to give, double it.

Dr. Mclaughlin:
Double it, yeah. (laughs) I agree.

Dr. Channick:
Yeah, if you say give 40, I'm going to say give 80 and so forth. It's a little bit facetious but...

Dr. Mclaughlin:
And give it IV, right? because they're not going to absorb it.

Dr. Channick:
Oh, yeah, yeah. I mean, I'm big on diuretic drips. They are easy to titrate, and you can always back off.

The next thing that we talk about—and I'll sort of lump the next two really—blood pressure and inotrope. I've been very impressed that these people I think sometimes are undertreated, and I've become very vigilant about what their blood pressure is, both on the systolic and MAP. Val talked about RV ischemia, which I think is a real issue due to right coronary hypoperfusion. As you recall, not to get too technical, but the right coronary artery is perfused throughout systole and diastole, unlike the left, which is only during diastole for the most part, but in a patient with very high right ventricular pressures, one can actually underfill the right coronary during systole, and so, therefore, it's a rationale for thinking about not just mean arterial pressure but systolic pressure as well.

We can debate on which pressor to use in these patients. I think that would be a debate that nobody would win because there's no real data on one pressor over the other. Do you have sort of an approach or a favorite? I like vasopressin. There's this theoretical issue that it may cause less pulmonary vasoconstriction than sympathomimetic drugs like norepinephrine. What do you think about that, Val?

Dr. Mclaughlin:
Yeah, I mean, like you said, Rich, it's all theory. Right? And so I think that's a fine choice. We certainly don't want to increase the heart rate too much because they do need the diastolic filling time because, as you were trying to explain with the coronary anatomy

physiology there, that the right ventricle should fill in both—should be perfusable in systole and diastole. In patients with pulmonary hypertension, their right ventricular systolic pressure can approach their aortic pressure, and they don't fill in systole at all, and then, as you increase their right ventricular filling pressures, you reduce the filling in diastole, which is the only place they are filling at that point, so you don't want their heart rate to get too fast so that you have more diastole to get that coronary perfusion to the right ventricle. Sometimes dopamine doesn't work as well for those reasons.

Dr. Channick:
Yeah, I agree. Tachycardia is always an issue. And in addition to the blood pressure and perfusion pressure, we talk about inotropes, and I like to separate that out when I'm thinking about it and teaching about it because there are drugs that obviously can directly increase contractility to the RV which heart failure doctors use. We use drugs like dobutamine and milrinone, which aren't pressors but inotropes, so I like to think about those as separate in a way, and we certainly use inotropic support quite frequently in addition to vasopressor support. Now, you can combine it with a drug like norepinephrine, but sometimes my approach is you give a pure pressor, like phenylephrine or vasopressin, and then a pure inotrope following things like central venous saturations, etc., etc. I mean, what is your sort of style with that?

Dr. Mclaughlin:
Yeah, I think what you said is really reasonable, Rich. The other thing I would add—and I know you're going to get to it—is that in pulmonary hypertension, in pulmonary arterial hypertension, IV epoprostenol is, I think, inotropic in these situations, and so sometimes that, in addition to being a pulmonary vasodilator, may get rid of afterload, as you say so promptly is the main problem, but many of us think that they have inotropic effects, the prostacyclins have inotropic effects as well.

Dr. Channick:
Yeah, and that raises a question and something that I always sort of wrestle with. In these patients, these sort of super-sick patients who are on some pressors, at what point do you pull the trigger on IV Epo if they are not already on it knowing that you can get some hypotension with it? I mean, what's your... This is sort of a little bit in the weeds, but when would you start a patient like this on Epo? Do you start low-dose up front or wait until your blood pressure is better or what?

Dr. Mclaughlin:
Yeah, I mean, I think it's highly individualized, but I think many such patients as you're describing are going to get better with Epo, and if you support their blood pressure and get them on Epo, I tend to try to do it earlier if it's feasible.

Dr. Channick:
Yeah, me too. And then finally, afterload reduction, which obviously is ultimately the problem, if you can lower pulmonary vascular resistance to improve RV function along with all the other supportive care, and to do that, we have a number of options. Again, this patient is already on oral PH medicine. We talked about IV epoprostenol. Again, the one concern is that you don't make them more hypotensive with systemic vasodilating effects. And then there's this really theoretical—I'm not sure proven—issue of worsening V/Q matching by giving a nonspecific pulmonary vasodilator, but at Reagan—I don't know what you do at Michigan—we put these people fairly frequently on inhaled vasodilators right up front almost coming in the door with either NO or an inhaled epoprostenol—again, little data to guide which is better. Obviously, watch out for things like the patient has mixed shock with a left-sided failure.

Dr. Mclaughlin:
Right.

Dr. Channick:
What do you think about that, Val?

Dr. Mclaughlin:
Yeah, we use nitric and are really migrating more towards inhaled Epo as well just because of the cost thing that you mentioned. I guess I would ask you… It's a good point to ask the question about what sort of monitoring these folks need. Obviously, they need an arterial line. You mentioned CVP. Do you actually put a Swan in these folks and leave a Swan in during their course?

Dr. Channick:
I really rarely do, and our ICU attendings will say, "Well, why can't we just put a line in or a Swan in?" I'm like it's really probably not going to change what we do because we kind of know what we're going to find. We already have a patient with **Q-V*** or PH. I think you can get reasonable surrogate for cardiac output with central venous saturation and CVP and the other biomarkers and avoid having a PA catheter, so I'm just not sure how it will change management in a patient like this. Do you agree?

Dr. Mclaughlin:
Yeah, I agree, but the key is you have to have an art line; you have to have a CVP. Those are actually critical.

Dr. Channick:
Absolutely.

Dr. Mclaughlin:
And then I think if you're worried that they have gotten mixed disease, if their left heart filling pressures are high for whatever reason or if a patient gets worse as you escalate pulmonary vasodilators and you're worried that you're putting them into pulmonary edema, there may be other reasons that you want to get it, but for the more clearcut group 1 PAH patients, we often get by with just the CVP and the art line.

Dr. Channick:
Yeah, agree, as usual. And then finally, the optional mechanical support, which obviously has gained popularity, the circuits have gotten better, and the ability to get a patient on to VA-ECMO or even central cannulation is there. Obviously, in a specialized center, you want to have that option. We question the use of RVAD, and we've been asked about that, although I'm not impressed that that has a real role in this type of patient due to the very high PVR. And then the question of what's the endpoint of ECMO. Is it only in patients who are waiting for transplant or could actually be a bridge to recovery? When should we pull the trigger? Because you obviously will face the dilemma in some cases of not being able to come off. What do you think?

Dr. Mclaughlin:
Right. I mean, it's obviously a bridge to transplant, but I think if you've identified a reversible cause, if they have an infection, if there's something that's reversible, it could be a bridge to recovery in those patients.

Rich, while we're on this topic here, there are a couple questions that might be appropriate to answer now. One was about hemofiltration, and one was about whether you've seen pulmonary edema with the use of inhaled Epo or inhaled nitric oxide. Do you just want to briefly answer those?

Dr. Channick:
Yeah, yeah, two great questions. So, yeah, the use of CRRT type of technologies is something, yeah, we're actually pretty aggressive with in patients. I'll use ultrafiltration, or in some cases actual dialysis is something that we pull the trigger on I think fairly early in a patient who's not really promptly diuresing with your aggressive IV diuresis. Yeah, I have 2 or 3 patients right now that are getting ultrafiltrated for fluid removal, and it's obviously a very effective adjunct. And then in terms of pulmonary edema, as we kind of eluded to, in the patients who do have some left heart issues, possibly patients with PVOD, you could potentially by increasing pulmonary blood flow worsen pulmonary edema, but the nice thing about inhaled NO and really Epo is it's very, very short-acting, and so, if you're seeing an adverse event like that, you can shut it off, and it goes away very quickly.

Dr. Mclaughlin:
Great. So, what happened to your patient?

Dr. Channick:
Yeah, so we did all the things that we were both talking about in terms of lining her up. Again, she was quite sick, CVP of 16, central venous sat of 52%. We started her on pressors with vasopressin as well as milrinone. For low cardiac output, we started a Lasix drip. We did give her inhaled nitric oxide, and we empirically treated her for pneumonia given the left lower lobe infiltrate. She improved, and we were very happy with the response to diuretics and supportive care, and you can see here improvement in hemodynamics, decrease in CVP to 8. We did start IV epoprostenol, which we slowly titrated, and then we weaned off the NO, the milrinone and vasopressin over 3 to 5 days, and she was discharged on day 12 doing very, very well on IV Epo as well as her underlying treatments, and a month after discharge, she is doing absolutely beautifully.

Dr. Mclaughlin:
Well, what a wonderful story.

Dr. Channick:
Yeah. I mean, one thing we learned—I've learned doing this for a long time, as well as you have—is that these people you can save. There are a lot of things we do in critical care that we sometimes feel we are doing futile care, but these are patients that, if you do your best critical care based on physiologic principles, you can get them through and get them back to where they were. So with that I'll...

Dr. Mclaughlin:
Yeah, so I...

Dr. Channick:
Go ahead.

Dr. Mclaughlin:
Go ahead.

Dr. Channick:
No, I'll turn it over to you now to kind of go through some other stuff.

Dr. Mclaughlin:
Okay, great. When you talk about making the diagnosis and getting it right, I mean, I think, fortunately, the cases that we get shipped to us in cardiogenic shock or bad right ventricular failure are few and far between. Most of the patients that we see we do the usual outpatient workup, and the echocardiogram is really a cornerstone. It's, in fact, what gets most of the patients into our office, right? Of course they estimate a pulmonary artery pressure on an echocardiogram, but in my opinion that's not one of the most important things in terms of determining the severity of the pulmonary hypertension. It's really taking a good look at that right ventricle, the size, the function, how the right ventricle interacts with the left ventricle, really that motion of that interventricular septum. Does the left ventricle still own it and the left ventricle looks like a doughnut or a bagel, or is the right ventricle starting to take over and you get that D-shaped septum? So I think that's really important to look at.

Of course, group 1 PAH is rare, and so you also want to look at the left heart, of course. Most of the patients with pulmonary hypertension on echocardiograms have elevated left heart filling pressures due to left heart disease, systolic dysfunction, diastolic dysfunction, valvular heart disease, and the Echo is wonderful for looking at all of that. We often do a bubble study with the very first Echo that we do on a PAH referral to look for, perhaps, a missed congenital heart defect, and it's important to assess whether or not they have a pericardial effusion because that has quite important prognostic signs.

Now, the right heart catheterization is required to make a diagnosis of PAH. We already talked about the hemodynamic definition, and you can't make that diagnosis without the PAH—or without the right heart catheterization. Of course, you look for the other etiologies. You can do a shunt run if you suspect congenital heart disease. It's really critical to measure the left heart filling pressure. And, in fact, it's really critical that that first right heart catheterization be really meticulous and measure saturation, measure not just pulmonary artery pressure but right atrial pressure, left heart filling pressure. You have to have a good wedge pressure tracing, and if you don't have a good wedge pressure tracing, sometimes you need to directly measure a left ventricular and diastolic pressure. Of course, you need to measure cardiac output, and then you have all the information you need to calculate a pulmonary vascular resistance. At the time of that first right heart catheterization, it's very important to do a vasodilator challenge, particularly in those patients with idiopathic heritable or PAH-associated with drugs and toxins to assess which patients might be appropriate for calcium channel blockers, so it's very important to do a thoughtful, meticulous right heart catheterization.

Rich, you spend a fair amount of time in the cath lab. Anything you want to add to that?

Dr. Channick:
No. I mean, you said it perfectly. How you interpret these wave forms and hemodynamics is obviously critical, and I think experience with a right heart cath, not just performing it but interpreting where in the respiratory cycle you measure things, and we see patients where there's huge swings, and making sure transducers are leveled and zeroed, shows the little things make a big difference.

Dr. Mclaughlin:
Yeah, those are all really great points. Thank you, Rich. And of course, before you get to the cath lab, you've probably also done PFTs and investigation for parenchymal lung disease. You've probably already done the ventilation perfusion scan. You have to do all the rest of the diagnostic workup as well.

And then the functional impairment of PAH, it's really multifaceted. The patients come to us because they can't do the things that they enjoy doing; they have reduced exercise capacity; they are struggling with their daily life. But then this diagnosis can also result in a number of other impairments like, Can they travel? They are on complicated medications. What's their prognosis? Do they get depressed? Do they start having problems with sleep? What happens to their relationships, their loved ones, the social impact of this? Losing control? Can they work? It really takes a great toll, and I think that's one of the reasons it's very important to be at a center that has the really multidisciplinary group. I can't say enough about how much time our nursing staff spends with these patients and all the other supportive allied healthcare professionals that we have take care of these patients.

Dr. Channick:
Absolutely.

Dr. Mclaughlin:
So, Rich, let's say we've made a diagnosis. What's the next step in assessing their risk?

Dr. Channick:
Yeah, what we know, Val, is that risk assessment is critical, and as with many diseases, determining where a patient fits on the risk scale is really important to make treatment decisions and follow up. There is a lot of work that's come out on this in the last few years really defining a number of parameters that seem to correlate with outcome, and this is a very commonly used table of various markers of risk that put a patient to low, intermediate or high risk, and most of these are fairly intuitive you'd think, obviously functional class, 6-minute-walk distance, exercise capacity, (NT)-pro BNP—you can see the list here—but to that end, several groups have looked at scoring systems, and this is one that's emerged as a very powerful tool, the REVEAL Calculator 2.0, where one can quantify risk using a number of parameters—and not to get into the weeds here in the interest of time—but a number of these markers, and that can be looked at not just at baseline now but at follow-up visits, and I think that's the important point.

There were 3 European-based registries that I would direct you to, which do very similar things in terms of looking at various parameters and coming up with a risk score, putting a patient to low, intermediate or high risk, with the purpose of really following patients. You can see on these Kaplan-Meier curves that whether a patient has gone to low, intermediate or high risk based on various systems of scoring, it separated their prognostic prediction very nicely, and not just at baseline but maybe more importantly at follow-up. And this sort of gets to what we tell patients is that we don't really know what your prognosis is on day one. We can tell you more after we see how you responded to medication. And so the recommendation to do risk assessment at every follow-up evaluation I think is a pretty hard recommendation and a very powerful one. That's, I think, incorporated into most, if not all, of our practices, and I could tell you personally that I don't think I did it very well up until these data really convinced me that we need to have a systematic approach to risk assessment.

Val, what do you think of that?

Dr. Mclaughlin:
Yeah, I absolutely agree. My quote that even my dear colleague Ray Benza loved is, "Every interaction is an opportunity to assess risk." Every time we see the patient we should be doing it, and it's very easy to do. The REVEAL Risk Calculator may be a little bit more complex, may take a little bit more time, but you can do the French noninvasive approach using 3 fingers in the office whenever you see a patient, so you count. Are they Functional Class I or II? Is their heart walk over 440? And is their BNP normal? And I don't know about you, Rich. I do all of those things at every office visit for a PAH patient, so I think you can assess the risk at every clinic visit.

Dr. Channick:
Yeah, completely agree.

Dr. Mclaughlin:
Okay. So let's move into treatment options. I think this has been one of the most exciting aspects of my involvement in PAH over about 2 decades now, and I think Rich is similar. When we first started, there was nothing, and then there was 1 drug for many, many years. It was IV epoprostenol. And over the course of the past couple of decades, we now have more than a dozen FDA-approved therapies for group 1 PAH, and they are depicted on this slide and can be divided up into really 3 mechanisms of action. The endothelin pathway—and the problem here is patients with PAH make too much endothelin-1, which is a potent vasoconstrictor which works on the endothelin A and B receptors on the smooth muscle cells, and we can block the effects of endothelin with oral medications that block those receptors. In the middle you see the nitric oxide pathway. The problem here is there is a deficiency of nitric oxide synthase in these patients, and so we can attack this pathway by either inhibiting the PDE pathway so we reduce the hydrolysis of cyclic GMP, or we can directly stimulate cyclic GMP with Riocogiat **direct to sGC stimulator*35:30** And then on the right, the longest-standing pathway that we've had, the prostacyclin pathway, there's a deficiency in prostacyclin synthase which converts arachidonic acid into prostacyclin I2. There are a number of prostacyclin analogs that we have that can be delivered either IV, subQ, inhaled or orally, and then there is one agent, an IP receptor agonist, that works on the same pathway but via a different mechanism of action, so we have many, many choices now. And listed here you will see the currently FDA-approved therapies and the categories that they fall into, so it's really wonderful to have all of these choices.

The endothelin receptor antagonist, there are 3 that are commercially approved. Of course, we have to monitor certain things, pregnancy. Bosentan is the only one that still requires monthly LFT monitoring. That's not on the label for macitentan or ambrisentan, although I think many of us still check LFTs on a periodic basis. I'll do it quarterly or so in those patients, and you need to check hemoglobin periodically as well. The agents that affect the nitric oxide pathway, 2 of the PDE5 inhibitors have the indication, vardenafil and tadalafil, and then there's one sGC stimulator, Riocogiat. These are all approved for PAH. I would add that Riocogiat is also approved for CTAP that is either persistent 6 months after endarterectomy or inoperable. And then the prostacyclin pathway, again there's continuous IV, continuous subQ, inhaled, oral, and then the oral IP receptor agonists and lots of wonderful data on the

prostacyclin pathway.

The treatment algorithm is depicted here, and it's really based on risk, as Rich so nicely described to you earlier. Step 1 is you need to make sure the diagnosis is correct. We've tried to highlight that. Step 2 is for those particular subgroups who might be vasoreactive and might be appropriate for calcium channel blockers. It's a very small proportion of patients. And then if you're not vasoreactive, what is your risk? If you're in the very highest risk category based on the information that Rich shared earlier, you need to be on very aggressive therapy that is going to include upfront combination therapy that includes a parenteral prostacyclin. If you're at low or intermediate risk, the majority of the patients are getting initial oral combination therapy, but that's really step 1, and probably even more important than that step is what happens at that next follow-up. You have to have a structured follow-up at the 3- to 6-month time frame. I'm doing mine closer to the 3-month time frame at this point in time. And if you don't meet the criteria for low risk, you need to do something different. You need to escalate. And whether that's add a second agent if you started with one or a third agent if you started with 2 or go from a less invasive to a more invasive prostacyclin, you need to do something to try and drive that patient into a low-risk status. The goal should be to achieve and maintain a low-risk status.

Rich, is that generally your approach as well?

Dr. Channick:
Yeah, absolutely. It's, again, gotten more aggressive as we look at data and on prognosis in patients who are on a low-risk status, so, yeah, that's our goal. We communicate that very clear to the patients. And I think when we talk about the need for additional therapies with patients, that's sort of how we communicate it to them, that if we get you to that low-risk status, not only will you feel better but you'll have a better outcome.

Dr. Mclaughlin:
Right, your likelihood of having an event of being hospitalized, dying, that sort of thing is lower. Now, we focus on all these special therapies because we've gotten very excited about them over the years, we've done lots of research, but it's really important to mention what the supportive therapies are. We, in fact, use anticoagulation very little right now. It used to be what we offered to patients with primary pulmonary hypertension based on some observational data, but I think in the current era with all of the PAH-targeted therapies that we've had, registries don't show as much of a benefit, so I've actually taken many of my patients off of anticoagulation. What about you, Rich?

Dr. Channick:
Yeah, absolutely. Obviously, bleeding risk and the lack of clear benefit doesn't really favor having most patients on it. Occasionally, patients who have indwelling catheters, who have intracardiac shunts, things like that, we may worry a little bit more.

Dr. Mclaughlin:
Yeah, good point. Supplemental oxygen therapy—oxygen is a vasoconstrictor, right? So again, there's that occasional patient with an intracardiac shunt that you're not going to be able to correct their saturations with oxygen, but in the majority of the rest of the patients, you should try to give them oxygen to maintain their saturation in the 90s, and you have to think about it not just at rest but also with exercise, sleep and altitude. We spoke a lot about diuretics for the case that Rich presented, but even in the rest of our patients, even in our more stable outpatients, we want to try to maintain their diuretics to keep them euvolemic, to keep their right atrial pressure near normal. Exercise I think is something that's overlooked. Sometimes these patients are very short of breath, they don't think they can exercise, or sometimes doctors are afraid to have them exercise, but there's lots of data that show a supervised rehabilitation, pulmonary or cardiac rehabilitation, can really improve their exercise tolerance, and we really try to encourage our patients to get into an exercise program. We don't want them to do any heavy weightlifting where they might have to Valsalva that can make them have syncope, but we want them to do low-level, graded aerobic exercise. Talking about pregnancy and contraception is very, very important. These patients have a high risk of both maternal and fetal mortality with pregnancies, and so we need to address that head-on. And then, again, the incidence of depression is high. The psychiatric implications are very substantial, so it's important to assess those as well.

Now, I think monitoring is the key. Rich talked about risk assessment, and we were talking about driving patients into a low-risk status, and so it is important to continuously monitor these patients. As I said, in the office you can do a clinical assessment. You can always do a functional class. You're asking about syncope. You're asking about progression of symptoms. You're examining them for right ventricular failure. In my clinic we do a hall walk with just about every visit. Some I do more sophisticated exercise tests, such as a cardiopulmonary exercise test. We'll get biomarkers at every visit as well. And then I think there's more variation at the frequency the other tests are being performed. We'll do an Echo at least once a year or more frequently if the patient has concerning symptoms, and then again, there's a lot of variation with which a right heart catheterization is repeated. I certainly repeat it sometime in the first 6 to 12 months in most of my patients just, again, to do that more formalized risk assessment, but if they are at low risk at that point, I may not

regularly repeat the heart catheterization.

Rich, how do you approach some of those more variable tests? How frequently do you do Echos and cath?

Dr. Channick:
Yeah, I certainly think very similar to you as well, the Echos sort of for a 4-month period. Repeat cath is sort of, again, very patient-dependent. If I'm concerned the patient is not doing well and may need even parenteral therapy added on or I'm just not sure, then I'll re-cath them. I would say most patients get at least one **(inaudible)*44:10** cath around 6 months, and then after that it's kind of variable.

Dr. Mclaughlin:
Great. Let's go on to another case. This is a patient of mine. She's 37. She has Sjogren's. I met her first in May 2017, at which time she had a 6-month history of progressive dyspnea. I characterized her as Functional Class III at the time. She had occasional palpitations, but the rest of her review of systems was unremarkable, and she really didn't have any other past medical or surgical history.

Her physical examination was consistent with pulmonary arterial hypertension. Her vitals were normal, as you can see there. Her carotid upstrokes were reduced. Her JVP was a little bit high. She had a palpable right ventricular heave, a loud pulmonic component to her second heart sound and a tricuspid regurgitant murmur. We methodically did the evaluation that included an echocardiogram, which demonstrated moderate right ventricular enlargement and dysfunction in RV pressure overload pattern, an estimated RVSP of 85. Her hall walk was 350, but this is something that I feel is really important. We have that magic number of 440 in all the risk assessments, but I feel like you need to put hall walks in context with the expected for that patient's age, gender and height. While 350 may be okay for some, this young woman had a predicted of 650, so it tells me she's really markedly impaired. Her V-Q was normal. Her PFT showed normal values in flows. Her DL was low, as we sometimes see in the connective tissue disease patients, so we did a chest CT, a high-res CT. That did not show ILD. Her HIV was negative. Her LFTs were normal, and her BNP was 320. And then here are her hemodynamics. Her right atrial pressure was 7. Her mean pulmonary artery pressure was 58–I'm sorry, 56–and did not change with nitric oxide. Her wedge was 8. Her cardiac index was a little bit on the low side, about 2.4, so her PVR calculated to 12.4 Wood units, so pretty sick lady.

In the old days, this woman would have gone directly on to parenteral therapy, and we did talk about that, but I feel a little bit more comfortable with careful, careful follow-up starting patients on upfront oral combination therapy, so she was started on an ERA and PDE5. We saw her at 3 months. She was improved, but I would still call her Functional Class III. Her hall walk had improved a smidge, 385, but still far from our goal of 440 and even farther from the predicted for her age and height. Her BNP was better but still high. She is still not meeting low-risk criteria, so it was at that point that a parenteral prostacyclin was added.

So, Rich, I think what we have done with this patient was really consistent with the evolving treatment paradigm.

Dr. Channick:
Yeah, absolutely, and I would just applaud how you managed a case like this, and really, for the audience, that it's all about the follow-up and the closeness and rigorousness of the follow-up for a patient like this because it could have gone 1 of 2 ways. Obviously, she could have gotten a lot better, or she could not have gotten a lot better, which happened in your case, and if that patient was lost to follow-up and just was on 2 oral medications, you could have had an adverse outcome, so that's the key message, I think.

Just sort of in closing—and then we do have, I think ,a couple questions here—and this is really by way of review, we really have evolved in how we treat pulmonary hypertension now, and it's really a testament to the development of therapies and effective therapies. In the past when we had 1 drug available, we just had 1 choice, and then as more drugs became available that worked through different pathways, we had the option of adding drug 2 to drug 1 and then drug 3 to drug 1, 2, or 3, and that may be a reasonable approach still in some patients, sequential combination therapy. There are very good studies that show that benefit with add-on therapies, ERA or prostacyclin pathway agents.

But I think more recently we, I think, have evolved to the concept of combination therapy upfront, and that's a paradigm that does get some fairly strong recommendation in the World Symposium that Val eluded to with the algorithm for most patients for combination therapy. There's the AMBITION trial, which is one study that kind of showed that. We're not going to get into any details in the interest of time except to say this was sort of the first upfront combination therapy randomized trial where patients were assigned to getting either ambrisentan or tadalafil or the combination, so a 3-arm study, and they looked at time to clinical improvement essentially. So a patient didn't just get worse, but they reached some clinical threshold of functional class and 6-minute walk distance, etc., and so that's basically what was shown here. This was a really a landmark study in that context of being 2 drugs upfront versus either one alone and then the clinical combination endpoint that was looked at in this trial of an inadequate clinical response.

In fact—this is laid out here—they were able to show that this approach of combination therapy upfront did lead to a significant risk

reduction compared to monotherapy, and this was pooled monotherapy with either ambrisentan or tadalafil, so you can see that almost 50% relative risk reduction, which was certainly quite a powerful finding. When they looked at specifically hospitalizations, you can see here similar robust results, a reduction in need for hospitalization with the combination approach. And we've seen this in other trials as well—the SERAPHIN trial with macitentan, the GRIPHON trial with selexipag—where this combination approach seems to be associated with a reduction in hospitalization for PAH. That, I think, is an important endpoint and one that we're seeing emerge from these various trials.

Finally, wrapping up with lung transplantation, although we do have these effective therapies... I'm sorry, there's literally a jackhammer going off outside my window now. We almost made it through.

Dr. Mclaughlin:
(inaudible)...*51:35

Dr. Channick:
We've had a few of those and the jackhammer. Lung transplantation still does have a role, and the lung transplant has evolved. Certainly, the need for lung transplant has decreased in the era of multiple effective medical therapies, but we still have patients in whom lung transplant is important as an option if they are not doing well or meeting treatment goals on medical therapy.

The question comes up, Val, what is the timing of a lung transplant referral or a listing? I mean, how do you approach it?

Dr. Mclaughlin:
Yeah, I think that's an even trickier question now with the LAS score and how that impacts things. I think the World Symposium algorithm was really meant to be something that could be applied across the world, and I think the lung allocation systems are different in all different places. Back in the day we used to just put people on the list to gather time because that was the only thing that mattered. Now my lung transplant folks don't really want to evaluate patients unless they still have Functional Class III symptoms and a suboptimal hall walk on lots of medical therapy, so I think there's probably a lot of institutional variation in how to manage those referrals, but certainly, if a patient is still at intermediate or high risk despite all the aggressive therapies that we have tried for the PAH, the lung transplant team should be involved. It may be different at other institutions. How do you handle it, Rich?

Dr. Channick:
Yeah, I think very similarly. I mean, I think… We have a very busy lung transplant program—I think they did over 100 last year—and so the waiting time is actually relatively short once patients are listed, so I think we have the luxury in some ways of really waiting until we see how they are doing on maximum medical therapy, and we're not usually too late once we list them there. In most cases we'll get the transplant in a relatively short period of time, so that works for our program. We obviously have patients who aren't going to be transplant candidates because of their BMIs or age, those kind of things, but for the young patient that's otherwise a good candidate, we'll wait until they're on parenteral therapy and then at least get them evaluated and then go from there.

Dr. Mclaughlin:
What about reflux in scleroderma, esophageal dysmotility? That's a challenge for us sometimes.

Dr. Channick:
Yeah, it's a huge problem, and again, we have some aggressive approaches with intervention to try to reduce the reflux. I think the experience of the UCLA program, which has a lot of scleroderma patients, has been actually relatively okay with maximum reflux management and have not seen a lot of major problems with the donor lungs afterwards, but it is a problem there's no easy answer to.

Quality of life is listed here just because really to remind us that in the end it really is about quality of life. Although quality of life has not been an endpoint that really has led to approval of any of these treatments, it really is in some ways the most important endpoint because if a patient's hemodynamics are better or their BNP is lower, does that really matter if their quality of life is not better? And there are emerging studies and data on improvement of quality of life with these therapies, but I think it's just sort of a call to really look at things like quality of life, home, activity monitoring, those kind of patient-centered metrics to evaluate our therapies going forward.

Dr. Mclaughlin:
Well, Rich, it was such a pleasure doing this program with you. I enjoy working with you. I learn from you every time I do something with you, so thanks for doing this with me. And I'd also like to thank the audience for taking the time to join us today as well. Everyone, stay safe, and I hope to see you soon for another program.