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Pulmonary Hypertension for Advanced Practice Providers: Risk Stratification and Diagnosis to Enhance Quality of Care and Outcomes

Announcer:
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Dr. Kingman:
Hello and welcome, everyone, to our program today which is entitled ***Pulmonary Hypertension for Advanced Practice Providers: Risk Stratification and Diagnosis to Enhance Quality of Care and Outcomes***. I'm Martha Kingman. I'm a nurse practitioner. I recently retired, which is awesome, from the University of Texas in Dallas after 24 years treating pulmonary hypertension patients.

Susie?

Dr. McDevitt:
Hi, everyone. Thank you so much for joining. My name is Susie McDevitt, and I'm a nurse practitioner at the University of Michigan Pulmonary Hypertension Program.

Dr. Kingman:
Great. Okay. I just want to go over our learning objectives for the next hour. We're going to talk about pulmonary hypertension, how we diagnose and treat it, as well as some updates from the recent World Symposium. We'll talk about signs and symptoms of pulmonary hypertension, tools to use to risk stratify patients, and then we'll touch a little bit on communicating with patients and referring physicians and the importance of getting patients to a pulmonary hypertension center early.

We're going to do this in a case-based format. I'm going to go through one case and then Susie will do another case. So there'll be 2 cases. They're quite different cases, but both of them typical of what we see often in pulmonary hypertension clinics.

So I'll get started. My patient is a 58-year-old female. And this is her medical history. She was diagnosed with scleroderma, more recently termed systemic sclerosis, but I tend to say scleroderma and both of those can be interchangeable. But she was diagnosed 4 years ago. She also has irritable bowel syndrome, stage 2 chronic kidney disease, and no interstitial lung disease.

For the past year, she's had slowly progressive shortness of breath, which she notices mainly walking up stairs, doing housework. She saw her primary care doctor who thought she should lose weight and do some exercising, and she did both of those things and continued to get more short of breath. She denies any chest pain, palpitations, syncope. She does have some mild swelling in her lower legs.

She follows up with the rheumatologist for her scleroderma, who did a DETECT algorithm and referred her to the pulmonary hypertension center. And I will tell you shortly what that DETECT algorithm means. She has no medication allergies. The only medication she's on is nitroglycerin ointment, which she uses on her fingers for her digital ulcers and circulation. She has no family

history of pulmonary hypertension and no family members with any rheumatologic disorders. She's never had a PE and denies any stimulant use.

Social history-wise, she works in a rural community as a fundraiser, as she does have poor or unreliable internet access, which is unfortunately pretty common, as many of you probably know.

On physical exam, her lungs are clear, her heart does have a faint 2/6 holosystolic murmur. Her abdomen's normal, benign. She has 1+ lower extremity edema. She does have digital ulcers, sclerodactyly, and telangiectasia, which we often see in scleroderma patients. And if you look at the pictures there, you can see the tips of 2 of her fingers have digital ulcers. And then she has these little red spots on her lips, which are the telangiectasia.

So we did routine testing and her 6-minute walk test was a little low, 385 m, and she did not require oxygen. Her SAT at the lowest was 93%. She's functional class III. Her blood work showed some anemia, hemoglobin of 9.1. She did have a positive SCL 70 and anticentromere antibody, a positive ANA and a creatinine of 0.8. Her NT-ProBNP was elevated at 650, and then on pulmonary function test, her force vital capacity was 92%. Her ratio was normal. She did have a mildly reduced total lung capacity, and her DLCO was 50%, which was significantly out of proportion to her normal forced vital capacity.

The VQ scan is shown here. There was no perfusion abnormalities. In PAH, you sometimes see this kind of mottled appearance on the ventilation and perfusion films, but that is more indicated of a PAH patient. There's no evidence there for CTEPH. And we did repeat the high-resolution CT scan of her chest, which did not show interstitial lung disease, and she did not desaturate on overnight oximetry testing.

And I mentioned that a rheumatologist did the DETECT algorithm, which is a really nice way to identify patients with scleroderma early so that they can get referred to the pH center. There's 2 steps to it. The first step looks at certain variables that are listed there in the gray box. They look at the pulmonary function test, whether they have telangiectasias or not, their NT-ProBNP, their urate, the EKG. And based on those parameters, they plug it into a calculator and that tells them if the number is high enough, that they need to have an echocardiogram.

So then you go over to step 2. They have had their echocardiogram, and then depending on what's seen in the echo, if there's evidence of pulmonary hypertension, then the patient is referred to the pulmonary hypertension center for right heart cath. And this patient's score was 42 and referred to the pulmonary hypertension center.

And this is her echocardiogram. And she has mild right atrial and right ventricular enlargement. Her LV and LA are normal. Her RVSP is estimated at 40. She has mildly reduced RV function and a mild pericardial effusion.

And then we did the right heart cath. These are her hemodynamics. Her right atrial pressure is 7, mean pulmonary artery pressure of 30. Her wedge pressure is 8, cardiac output 4.4 with an index of 2.7. SVO_2 is 64%, and her PVR came out to 5 Wood units. And then we diagnosed her as Group 1 pulmonary hypertension associated with scleroderma, what we refer to as CTD-PH.

And this is a pie graph on the left showing the overall breakdown of the types of pulmonary hypertension within Group 1. So half of them are idiopathic, about half, 46%, and then the other half are associated, 51%. So if you take the associated group and blow it up, which is the pie chart on the right, you can see that half of the associated conditions are connective tissue disease, 50%. And within the connective tissue disease category, scleroderma, of course, is the most common, but can also include mixed connective tissue disease, Sjögren's, lupus.

Okay. And this is a little bit of an older slide, but it's very interesting because it shows the difference in survival in a patient with scleroderma if they have pulmonary hypertension or they don't. And so the vertical axis is their survival and then this is out to 5 years. And if you look at the top bar, these are scleroderma patients without pulmonary hypertension, and it looks like about 80% or so alive at 5 years versus if they have pulmonary hypertension, their survival curve is terrible, down to about 10% at 5 years. So we try to, if we can, identify these patients early and be aggressive with their treatment.

So this is the ERS/ESC risk assessment approach. I think Susie's going to do REVEAL in hers, so we could just kind of review quickly both of these most common approaches. But in this one for the initial evaluation or the initial risk assessment, it means the 3-strata model. So patients are categorized as either low, intermediate, or high. And what we often find is what you see here. We have a smattering of things in different categories. You kind of have to look and see where do they mostly fall. And I want to make a comment on this first one, the signs of right heart failure. I wish that I wasn't involved in this, but that the middle one said mild. So you only have a choice of absent or present. And I really struggled with what to put on hers because she only has mildly reduced RV function and mild swelling in her legs, so somebody might have put her in the yellow category there.

But progression of symptoms is slow. Her symptoms have been going on for a year. She's not having syncope, she's functional class III. Her walk test fits in the intermediate. Her anti-proBNP fits in intermediate. So we get more in the intermediate category there. And then if we look at the second half of this model, her TAPSE – actually this no pericardial effusion should be the one in the middle with minimal pericardial effusion. But the TAPSE falls in low, so minimal pericardial effusion in the yellow, and then she didn't have a cardiac MRI. But on hemodynamics, also, this right atrial pressure should be below 8. Sorry, I thought we'd fixed that this morning. So this right atrial pressure should be in the low-risk category as well. So mostly on this last half, we've got low risk. So we've got intermediate, and we've got low, primarily.

So if we move on to the treatment algorithm, and this is the ERS/ESC treatment algorithm. And it was recently tweaked a little bit, which we will talk about when we go into the updates from the World Symposium. But at the time of this case study, this was the treatment guideline that we used. So this treatment guideline starts with treatment for patients who are idiopathic, heritable, drugs and toxins, or CTD related. Diagnosis is confirmed in a PH center. Vasoreactivity testing was negative, which is the case with our patient. General measures are instituted, so that would be something like Lasix for her swelling or if she needed oxygen, which she did not. And then you look at whether the patient has cardiopulmonary comorbidities or not. And this particular patient did not have cardiopulmonary comorbidity. Her HRCT was fine, there was no lung disease. There really wasn't any evidence of diastolic heart failure or high blood pressure, so no cardiac comorbidities either. So we went down the algorithm on the left side, which is patient without cardiopulmonary comorbidities. And we did her risk assessment, and she came out, I would say, looking at all that, in the low to intermediate category. And the treatment recommendation there is an initial ERA and a PDE5 inhibitor with regular follow-up. Repeat the risk assessment in 3 to 4 months.

And this was a sub-analysis from the AMBITION study. And I imagine most of you attending are familiar with AMBITION, but it was the study that proved that up-front combination therapy with an ERA and a PDE5 was superior to monotherapy alone. And this is a subset of that study that looked at the scleroderma patients. And on the vertical axis here, we have percent of patients that are event-free, and this is out to 168 weeks, which if my math is right, is about 3 years. And if you look at the combined patients who were started on the ERA and the PDE5, they have a much better percent of being event free, versus the pooled monotherapy. It was a 56% risk reduction.

So for general measures, we did start her on some furosemide and potassium supplement. We'll do a BMP in a week or 2 to just make sure her creatinine and her potassium are okay. We have been trying to initiate shared decision-making with patients, so we go through the options, and this patient, she agreed to macitentan and tadalafil. And the plan was for close follow-up in 3 months and at that point, if she was stable on both medications, tolerating both of them, that we would switch over to this new combination macitentan tadalafil pill. We did make note, though, that we're going to have to follow her in person each time because she has very unreliable internet access.

One point I want to make just before I end my case study, or wrap up mine, is that these patients with CTD often have overlap. And this particular case sounded like it was just scleroderma, and she didn't have anything else going on, and I would say, probably Susie would agree, most often we do see a little bit of overlap. And that can be overlapped with Group 3, because scleroderma patients, a lot of them get interstitial lung disease, they become hypoxic, and then as they age, a lot of scleroderma patients get diastolic heart failure, too. So you may see some overlap of Group 1, Group 2, Group 3, and that's really one of the reasons why patients should be in a pulmonary hypertension center where we can kind of sort out what's driving what.

Okay. So in summary, pulmonary arterial hypertension is a common complication of connective tissue diseases, especially scleroderma or systemic sclerosis. And when CTD complicates pulmonary hypertension, it's significantly worse in survival and is a leading cause of death in these patients. Early screening of at-risk patients with scleroderma and mixed connective tissue disease using DETECT algorithm improves outcomes, and aggressive treatment including combination therapy and close follow-up is recommended.

So that is my case. I'm going to turn it on over to Susie to go through hers.

Dr. McDevitt:
Okay. Wonderful, Martha, that was an excellent case example, and I just can't stress enough, I know you agree, the importance of the DETECT algorithm. And for us it's been amazing, doing that screening in those scleroderma patients every single year. We do that for patients even if they have normal right ventricles on echo and have functional class II, mild dyspnea, mild symptoms and take them to right heart cath when it's indicated, when that DETECT 2 score is positive. And we are finding earlier pulmonary vascular disease, so it's really been impactful and we so encourage all of you to be doing the same thing. So that was a great case example of that.

So my case is a recent case for us at University of Michigan. I wanted to make a few points. They're a little bit different than Martha's. This is a 42-year-old female, and we'll go through her medical history, physical exam, testing, echo, right heart cath, and then just her initial treatment. But this was a patient that probably, like many of us, sought care at her local small community hospital in northern

Michigan in a rural area. And she goes to the ER with chest pain, dyspnea, fluid retention, kind of those normal things. And she was transferred to our center, so we met her as an inpatient.

So her medical history, she had a history of DVTs which were considered provoked. It was while she was on oral contraception. She was not on chronic anticoagulation. She had a history of bipolar disorder, some polysubstance abuse. She had a one-time alcohol related pancreatitis. She had an incidental finding of a renal artery aneurysm, and she actually had one previous right great saphenous vein ablation. She had lived all over the country. Her medical care was kind of fragmented and had moved home to be near family, and so this was her list of medical histories. She got transferred to the University of Michigan with suspicion for, actually, Group 4, chronic thromboembolic pulmonary hypertension. She had a CT pulmonary angiogram, a CTPE, normal protocol that we all see all the time, that was positive and so she was transferred to us to evaluate for Group 4, CTEPH.

So upon my medical questioning and history-taking, I learned a lot more about her, and it was really pretty interesting to hear her whole history. So she has a high school education, she works as a waitress in a bar. She has quite low health literacy. Her living situation, as we said, is rural. She also has poor access to Wi-Fi at her home. She's a single mother of a 2-year-old with a disability. And I was able to really build a relationship with her and dive deeper into her polysubstance abuse. She had been smoking one pack a day of cigarettes since age 16. She had a remote cocaine history use. She was drinking about 4 alcoholic drinks a day at her job, that was kind of the normal culture at her bar where she worked, and reported much heavier previous consumption. And interestingly, she was using methamphetamine about 2 times a day, mostly by inhalation. She had not done IV drug use for many, many years, and she had been able to quit methamphetamine for up to 5 years at a time previously. And per her report, she was using meth, as we hear from other people, really for fatigue. She was using it 2 times a day due to significant fatigue trying to work and care for her 2-year-old. So she would use it in the morning to get her child off to daycare and she would come home from work and use it in the evening to take care of her child. And so it was pretty interesting because we were all sort of going down the rabbit hole and the algorithm of CTEPH until we learned this interesting detail about the methamphetamine use and consistent use.

She had quite fragmented primary care. Her family history, she did have a history of DVT in her father and no family history of pulmonary hypertension or rheumatologic conditions.

So her presenting symptoms, we deemed her as functional class III. She had dyspnea walking short distance room to room in her home, climbing stairs, carrying items such as groceries or her 2-year-old son, daily fatigue. She endorsed palpitations with exertion and when she lied down at night. She had occasional lightheadedness, so we would deem that as presyncope, but really no syncope. She did not have any PND or orthopnea, and she had lower extremity edema just for the past 3 months, so her symptoms were progressing.

In terms of her diagnostic tests that we obtained early on, her ECG, of course, normal sinus rhythm with the usual findings that we see with right ventricular dysfunction and strain. She had right axis deviation, right bundle branch block, RV hypertrophy and that nonspecific ST-wave abnormality that we see. And remember that any right axis deviation has such a high predictive value of pulmonary hypertension, so any right axis deviation warrants further investigation of pulmonary hypertension.

Her VQ scan, interestingly, was negative after she came to us with a positive CTPE. Her VQ scan was negative. We'll look at that in a moment. Laboratory studies were negative. Her ANA, her HIV was nonreactive, and in terms of her echocardiogram, her LV ejection fraction was normal at 60%. She had moderate TR. Her estimated RVSP was 77, based on an RA pressure of 3. Her right atrium and right ventricle were severely enlarged. She had moderately reduced RV systolic function. She had that flattening of the interventricular septum, which is evidence of RV pressure overload, and she also had a small pericardial effusion, similar to Martha's case.

Physical exam. She came to us a little volume-overloaded, so we did diurese her. But her physical exam, she has a normal blood pressure. Her heart rate's fine. BMI is 27.65. She is not hypoxic on room air. And her JVD is about 12 cm. She has no abnormal breath sounds. On physical exam cardiac-wise, she does have a palpable RV heave. She has a normal S1. She has that classic loud pulmonic component to the second heart sound, and she has some TR on auscultation, as well. She came in with some mild lower extremity edema, and she has no findings of connective tissue disease on her skin in terms of telangiectasias or sclerodactyly or digital ulcerations.

So her test results, these are kind of just coming right out of the grids that we use in our charts, so it's kind of easier to just put them in for you this way. But we got some new PFTs on her and you can see her FVC is just a little bit low. FEV1's a little bit low, and her DLCO is surprisingly not that reduced, but she does have mild impairment when it's corrected for hemoglobin.

And again, the VQ scan on the bottom, you can see on the left side a normal or pulmonary arterial hypertension VQ scan that we see, which has that diffuse patchy kind of appearance, which is kind of more indicative of the diffuse perfusion defects that we see in Group 1 PAH. On the right, you can see how different the VQ scan is in a chronic thromboembolic patient, with at least one segmental perfusion defect that, again, is inconsistent with the VQ scan findings, the ventilation findings.

Other test results. I'm just showing you here, her CT PE at the outside hospital did demonstrate this eccentric, mural-based low-attenuation material, left pulmonary artery, left lower lobe pulmonary arterial branch suspected to represent thrombus. And a lot of times, we have to redo testing and kind of really sort out what is the etiology? What is the cause of this right ventricular dysfunction in the patient?

So she has the CTP at the outside that's positive. She has a VQ for us that's negative. We wound up going ahead and getting a dual-energy CT scan. I don't know if your centers are doing this. We are a full CTEPH center, so when we have any question between some of our imaging, we will add in a dual-energy CT scan. And this was done to really help differentiate is there some chronic thromboembolic clot burden or material in there? So I'm not going to go in the weeds of all of this. But it did show that there might be some chronic PE in there with the DECT, so we wound up going ahead and pursuing not only a right heart catheterization, but also a pulmonary angiogram. And pulmonary angiogram, as you all know, is really, sort of the gold standard test to look for chronic thromboembolic disease.

Interestingly, her pulmonary angiogram – here's her report here. Mean pulmonary artery is widely patent, and, really, the vast majority of her vessels were widely patent. She has this distal arteriopathy all over, all of her vessels, right side, left side, A1 to A10, all show just this distal abnormal venous return that we consider just diffuse arteriopathy, or vasculopathy, that we see in advanced Group 1 pulmonary arterial hypertension. So we did put her through all of that testing because of her sort of abnormal findings on some of her results.

We talked about her echo earlier. She has a lot of TR. She has a low TAPSE, a low S prime. She has severe right ventricular enlargement, moderate RV, systolic dysfunction, enlarged right atrium, and that RV pressure overload. We know that pericardial effusion is a high-risk sign, an ominous sign, in pulmonary hypertension.

So here's her first right heart cath, which was done again after she was volume optimized. Of course, we recommend you get your patients volume optimized before you do your index right heart cath. And you can see she has a right atrial pressure of 8, a pulmonary capillary wedge pressure of 11. Her PA pressure is 79/40 with a mean of 53, so we know that's very, very high. And cardiac output and cardiac index are listed there. We use thermodilution. We measure by both thermodilution and Fick, but you can see her cardiac index by thermodilution is extremely low at 1.7, and she has no response to inhaled nitric oxide. Her resting pulmonary vascular resistance is 13 Wood units, so that's very elevated, of course.

So when we do our index risk evaluation for our patients, we do tend to use the REVEAL 2.0 risk calculator. Again, for your first risk evaluation, you want to use a comprehensive multiparameter tool that designates into this 3-stratification, as Martha mentioned. So patients will be deemed low, intermediate, or high risk, and you can absolutely use REVEAL 2.0. You can use ESC/ERS, as Martha presented. Anything that's comprehensive with lots of parameters. This one has 13 parameters, and you can see here, we've got them kind of circled there. Her subgroup, we're going to call her methamphetamine-associated pulmonary arterial hypertension. And then, her demographic, you put in her eGFR, her functional class III, blood pressure, heart rate, has she had a hospitalization? Yes. We often don't get a baseline 6-minute walk test if we meet the patient in the hospital and they're pretty sick and they have a low cardiac index and a very high PVR, especially in the setting of presyncope. Sometimes we'll forego that baseline 6-minute walk because it can be kind of risky. So she did not have a baseline 6-minute walk, so that is not taken into this calculator. Her NT-BNP is elevated. She has a pericardial effusion. Her DLCO is not markedly low, which is sometimes unusual, usually we see that low. She did not have a right atrial pressure greater than 20, and her PVR is not less than 5 Wood units. So very simple to use these risk calculators, to do them online and include them in your medical notes.

So her risk score at baseline is a 10, and just to remind you, the Reveal 2.0 risk score, low risk is 0 to 6, intermediate 7 to 8, and high risk greater than or equal to 9, so she's deemed high risk. And we can see on the graph there, the 1-year, 2-year, and 3-year mortality rate for those patients in low, intermediate, and high risk. So certainly, our goal is going to be to use medical therapy to improve her to low-risk status.

So just a quick slide about methamphetamine-associated pulmonary hypertension. We know it's severe. We know it's a progressive form of PAH and it's associated with poor outcomes. Urine drug screening is recommended for all patients now with idiopathic or any history of substance use disorder. We're just seeing more and more of this. I know Martha took care of many patients with meth-associated PAH. It may be a contributor, as we said, when screening now for people we thought maybe were idiopathic, we should be thinking about screening for meth.

We know that there's cardiovascular toxicity in terms of myocardial ischemia, infarction, cardiomyopathy, can have many respiratory consequences, pulmonary hemorrhage, pulmonary edema, lung injury, pneumothorax, etc., and pulmonary hypertension. We'll talk about, in a moment here, the updates from the World Symposium, but it is listed under drugs and toxin-associated PH, or PAH, as a

definite association. You can see methamphetamine there. And we know it's a highly addictive drug. It stimulates the release of catecholamines. We think about it as similar to the fenfluramine back in the day with diet pill-associated pulmonary arterial hypertension. So something we're really trying to learn more about. These patients are not included in our clinical trials, so it's unfortunate we don't have quite as much studied and robust data about treatment and outcomes. We do have data on these patients in our observational registries, but I'm sure a lot more to come on treatment and management of these patients.

So initial treatment for her, we diagnosed her with Group 1 pulmonary hypertension, or PAH associated with drug and toxin use. She is functional class III. We know her risk evaluation was high risk at the beginning. We had to do many, many things, as you can imagine, in a case like this. We had social work involved for community resources for her mental health wellness, social security disability, durable power of attorney. We needed support for cessation of her substance use, of course. We needed to talk about durable contraception for her. We wanted to try to connect her with a patient mentor and get her connected with support groups. We had to use shared decision-making, of course, regarding her PH medical therapy. The whole process of obtaining complex medications and using specialty pharmacy was a lot for her for sure. So it's easy and simple, of course, to always start a PDE5 inhibitor. We started that; that was no problem. We prescribed macitentan, and we get that started as soon as possible and, of course, insurance dictated choice B for her ERA, which was fine. We put her on a different ERA per her insurance's preference. And with shared decision-making, we decided she really was not a candidate for parenertal prostacyclin therapy at this time. With her social factors and her preferences, and some of our concerns, we decided together to start triple therapy and use inhaled prostacyclin, which wouldn't be really what's indicated on the guidelines for a high-risk patient. But we decided to follow her closely, start this, and we could make adjustments, if needed, in the future.

So, absolutely, close patient follow-up with frequent telehealth visits. We were visiting with her every 2 weeks after discharge to keep moving on getting her on these complex therapies and up-titrating her medications, managing those side effects. We plan to repeat an echo at 3 months, and we would be doing a repeat right heart cath pretty quickly, based on her clinical response, her echo findings, and her follow-up risk stratification.

And I'm happy to report today, that she's actually doing quite well on triple therapy. Her inhaled prostacyclin therapy is titrated to max dose and her follow-up echo is outstanding. So we'll be cathing her soon, and she's clinically doing really well, which is a great story. She has not completely stopped methamphetamine, although continues to try.

So, summary here, meth-associated PAH is a severe, progressive form of PAH with poor outcomes. We do talk to patients about the fact that if you continue to use methamphetamine, it's going to be really difficult to reverse and improve this pulmonary vascular disease and pulmonary hypertension. Close follow-up, frequent visits. We wanted to really build trust and promote adherence to her PH medical recommendations, and we really wanted to provide this comprehensive team approach in the setting of this high-risk social determinants of health with her multiple concerns and issues. Aggressive treatment including combination therapy and repeat risk stratification, of course, would be recommended in her case.

So, Martha, any comments about that case? That was a little different than yours, but I know we've seen many of those.

Dr. Kingman:
Yeah, that was a great case. Thank you. Yes, we have seen a lot. The only comment I would make is that we sort of made this, across the board, everybody gets a drug screen if they're diagnosed with Group 1 pulmonary hypertension. And it's surprising how many you find that are using meth that you wouldn't think would be using meth. So you can't really go by your gut.

Dr. McDevitt:
Right. So we're supporting her, cheerleading for her, and she's doing really well. So I'm going to stay very hopeful about that. So.

Okay, so we thought we would just take a moment to go through some of the updates from the 7th World Symposium. I think we're going to have discussion time at the end. So I'll go through the first few slides and then Martha's going to join in on some of the other updates.

So we just have kind of a little smattering of –

Dr. Kingman:
Hodgepodge.

Dr. McDevitt:
– hodgepodge of the key points. So I wanted to start with the patient perspective and remind you that during the 6th World Symposium in 2018, the importance of the patient perspective and the patient experience living with pulmonary hypertension was finally formally recognized. That was the first time it was really included. So the incorporation of the patient perspective in the 2022 guidelines was

amazing. It was a big step forward for all of us as healthcare professionals to be sure we're partnering with our patients and caring for them. So we want to make sure our patient, of course, is at the center of all considerations with respect to screening, diagnosis, treatment, patient education, advocacy, clinical trials, all components of care. So there's a really nice article in the whole summary in ERS from the World Symposium by this committee that worked on the patient perspective. It's a lovely summary. I highly recommend you all read that. So they talked about the importance of shared decision-making, so the patient has access to all information and education while working with their healthcare professionals to make the best choices about their care. Talk about the importance of multidisciplinary team support, which is essential, of course, to develop these comprehensive treatment plans that manage not only the medical aspects of pulmonary hypertension, but also their physical and mental well-being as well. And talks about how this burden of living with pulmonary hypertension is not just physical. How there's so much anxiety and depression for both the patients and the caregivers and how important it is to manage all of this and especially these emotional reactions as well. So really nice summary here.

It talks about the importance of thinking about including these patient-related outcomes in routine clinical care, which I think is a really interesting idea, and I think maybe we should all be thinking about moving forward in that way. We know that these patient-related outcome measures are included in the clinical trials and have been for some time, but these are wonderful quality indicators in our care that we can think about, and they describe ways that maybe we could include some of these in our routine clinical care when we see patients in clinic. So I think that is going to be a really exciting new field for us to try to think about, to add to our clinical care patients.

And this just shows you an overview of various factors and perspectives that affect and inform the patient's experience of living with the disease. Their access to care, global view. There's a lot of discussion about global view in this exact publication. It talks about how important patient associations and advocacy are, humanitarian emergencies, patients in research, supportive care, E-Health, all of these things that really impact the patient's experience. So it's an excellent, excellent paper.

In terms of classification, I didn't think there were tremendous updates. Did you, Martha? There were little tweaks, right? Maybe little tweaks?

Dr. Kingman:
Very small tweaks.

Dr. McDevitt:
The main way they describe that here, they talk about how the changes are small things, so they talk about reintroduction of long-term responders to calcium channel blockers. So the groups are the same, Group 1, 2, 3, 4, 5, and there's some small tweaks. So they've kind of changed the way they describe the calcium channel blocker responders here, and they term these long-term responders to sort of differentiate from the acute responders. So that's kind of a key point in that publication. In Group 2,they make some differentiations with Group 2 and Group 3 subgroups, and these are based on just some of the abnormalities with the diseases. You can see here, in Group 2, clarifying more of the heart failure, preserved ejection fraction, mildly reduced ejection fraction, or reduced cardiomyopathies with specific etiologies and really differentiating the valvular heart disease. And the Group 3 changes talk about these subgroups. Instead of just calling them restrictive or obstructive lung disease or combined restrictive and obstructive lung disease, we're now using the different phenotypes. We're talking about PH with COPD versus PH with ILD versus PH with combined pulmonary fibrosis emphysema. They also introduced the term nonparenchymal restrictive disorder, as well. So just small tweaks there. There are some additions to the drugs and toxins list, as well. A couple things there, mitomycin C and carfilzomib have been added into the list of drugs of definite, and they've changed the list of drugs and toxins in Group 1 to include definite or possible. They've changed the association with those drugs and toxins.

So I think just little small tweaks there. In terms of diagnosis, what did you think about the diagnostic algorithm, Martha? I think it's simplified. What did you think?

Dr. Kingman:
I thought so too. Much more straightforward, less boxes, less words. I like that.

Dr. McDevitt:
Yep. And so the way they talk about the diagnostic algorithm, they've tried to streamline it and make it a more step-wide approach. There's 5 steps, step 1, 2, 3, 4, 5.

And step 1, we do the normal thorough clinical history of the patient, symptoms, physical exam. They talk about, in this publication, the most frequent symptoms that your patients would have.

Step 2, it's just a basic investigation of simple noninvasive tools. That can start with chest X-ray, ECG, oxygen saturation, laboratory studies, BNP or NT-BNP, and again, they bring up the point of how important right axis deviation is.

And then step 3, we're getting into a more detailed evaluation of heart and lung, including the echocardiogram being the most important tool – noninvasive tool, looking at both left and right ventricular anatomy and function and valvular abnormalities. They talk specifically in this publication about the TR velocity, and we can read more about that and sort of the probability of pulmonary hypertension based on that TR velocity from echocardiogram. Step 3 also includes pulmonary investigation, so thinking about a blood gas, PFTs with DLCO, imaging and high-res chest CT would be preferred and thinking about overnight oximetry or a polysomnogram looking for hypoventilation syndromes. So all of that is part of step 3.

Step 4, of course, ruling out chronic thromboembolic disease. So this is where our VQ scan is our gold standard of choice to rule out chronic thromboembolic disease. And once we go through that step 5, if pulmonary hypertension is suspected based on these noninvasive measures, the patient should be referred to a PH expert center to evaluate all clinical information and perform that right heart catheterization. And of course, anytime throughout that evaluation if there is suspicion of high probability of PAH or CTEPH, the patient should be fast-tracked for referral for that evaluation.

So I think it's a more simple approach. They did take out this comorbidity portion that we saw in the ESC/ERS diagnostic approach, so it's really just taking all patients and going through this step-wide approach to diagnose with a fast-track as needed to PH referral center. So I think that's also a nice publication.

And I'll turn it over to Martha.

Dr. Kingman:
Okay. I'm going to talk about just a couple updates to the therapy algorithm. And first, they've listed out goals of therapy in this publication and they include, on the left-hand column, the domain, there should be a measure of exercise capacity, RV function, and hemodynamics when we're talking about our goals of therapy. And then in the first column to the right, the treatment goals are outlined specifically, what these goals should be. And the 6-minute walk test goal is greater than 440 m, and we want patients to be functional class I or II.

And then the comments and limitations there talk about, well, you may not be able to get every patient who has a poor walk test above 440 m because other things can impact that. If you've got somebody that's got a bad hip and bad back and they can barely walk, you're not going to get to 440. So you have to kind of take that into consideration, of course.

And then with regard to RV function, the goal for the BNP is less than 50 and the NT-ProBNP less than 300. And then they list some echo parameter goals too, but they don't really prioritize. They say that more research is needed to prioritize them, but the right atrial area should be less than 18. TR, you want no TR or trace. the TAPSE over systolic pulmonary artery pressure greater than 0.32. And then under hemodynamics, the goals are a right atrial pressure less than 8, a cardiac index greater than 2.5, a stroke volume index greater than 37, SVO_2 greater than 65%. We want the PVR less than 5.

And then also need more research to prioritize, but they recommend a goal of getting everybody's mean pulmonary artery pressure to less than 30 to 35 range. And then the pulmonary artery compliance, greater than or equal to 2.5.

And this is a new pathway slide. Those of you have been in pulmonary hypertension for a while know that for the last 2 decades we had 3 pathways, the endothelin pathway, nitric oxide pathway, and the prostacyclin pathway. We're all very familiar. Now we have the fourth pathway which is where sotatercept fits. And this is labeled activin/BMP pathway. I've also heard it referred to as ASI and activin signaling inhibitor pathway. And as you know, the sotatercept is in that pathway and it aims to rebalance the pro-proliferative and anti-proliferative properties that are out of balance in pulmonary hypertension, whereas our 3 prior pathways are all vasodilators. So this is very exciting to have something that is more than just a vasodilator and the PH community is very excited about this.

Okay, so this is the treatment algorithm. Also has been simplified and I like this. You start off, and this is therapy, same again, for PAH patients who are idiopathic, heritable, drugs and toxins, or CTD related. And you do their initial risk assessment and then it just breaks it down into not high risk or high risk.

So on the left, the not high risk, that would be your low or your intermediate patients would fall there. They're not high risk. They get a combination ERA and a PDE5 inhibitor. So similar to what we saw, but they de-emphasize monotherapy in this treatment algorithm. Remember, the one that I showed you in my case study had that right-hand column if they got comorbidities, where you might start them on monotherapy? They didn't even talk about that in this one. And then the high-risk patients, similar or the same, really, as our last iteration where patients are on an ERA, a PDE5, and a subcutaneous or intravenous prostacyclin medication.

And then, in 3 to 4 months, you repeat their risk assessment, reevaluate them. And as we saw previously, if they're low risk, great, you just continue doing what you're doing and continue to follow those patients to make sure they stay low risk. Now if they're intermediate-low – remember, at this point on reassessment, we use that 4-strata model where they split the intermediate group into intermediate-low

and intermediate-high. So if they're intermediate-low, after their reassessment, you can add on this ASI or an inhaled or oral prostacyclin, or you could switch the PDE5 to soluble guanylate cyclase stimulator. So you got quite a few options in the low intermediate. If the patient is deemed intermediate-high, then they should have an IV prostacyclin or some parenteral prostacyclin added or an ASI. And then, if they're high risk, they need to have IV therapy, if they haven't been on it already, an ERA, PDE5, and most likely they're going to end up being on 4 drugs with the ASI as well.

And then they added this persistent intermediate-high or high risk. Those patients are on maximal 4-drug therapy and then should consider lung transplant at that time.

Now on the right are these treatment algorithm key points that they make in the publication. And when I saw this first one, a, it really struck me as like, wow, this is for patients who have a mean pulmonary artery pressure greater than or equal to 25 and a PVR greater than 3 Wood units, which is our old definition of pulmonary hypertension. And the reason that they did that is because the clinical trials used the old definition of pulmonary hypertension. So we don't have good data on the 20 to 25 mean PA range or the PVR from 2 to 3. So that's why they chose to put that in there, because the data supports that.

And then risk assessment should be done at baseline and every 3 to 4 months thereafter. Functional class, walk test, and natriuretic peptide should be part of that risk calculator. Hemodynamics and RV imaging and other measures should also be done to supplement your risk assessment. I know for us, at least after we put somebody on dual or triple therapy, we actually do repeat their right heart cath in 3 months, in addition to an echo and a full risk assessment. So I think centers do things a little bit differently. Initial triple therapy with a parenteral prostacyclin is recommended in high-risk patients and may be considered in non-high-risk with severe hemodynamic or poor RV function. And then most low-risk patients, if they're low risk, they should continue their initial therapy and continue to be monitored.

And then there's a note here that clinical trials with oral and inhaled treprostinil included only patients on monotherapy, while studies of selexipag and sotatercept included patients on combination therapy. So that's just something to kind of keep in the back of your mind. And then transplant referral should be considered for select high-risk patients at the time of diagnosis and certainly if they remain in that persistent intermediate-high or high-risk category.

Susie, anything else to add about this updated treatment algorithm from your point of view?

Dr. McDevitt:
Nope. I think we were all kind of waiting to see where this new activin signaling inhibitor was going to fit in the algorithm based on the data and the evidence. And so you outlined that very nicely. It could be used here, here, or here, right? So.

Dr. Kingman:
Yeah. Really everywhere but low risk, right? If the patient's on ERA and a PDE5 and they stay low risk, then they wouldn't necessarily need the ASI, but everybody else has the option for that. Okay.

All right. And then we were going through all the publications. There's 17 publications from the World Symposium and so it's quite a bit of reading. But I thought this was really interesting and a little bit off topic here, but this is a slide that they put together for patients who have pulmonary hypertension due to fibrotic lung disease. So these are patients, you diagnose them with precapillary pulmonary hypertension and they have fibrosing interstitial lung disease. What do you do with these patients? And so I thought it was really nice that they have kind of created a little chart or some guideline to kind of direct you. So on the left, this column where it says favors no PH therapy, that's in the blue. Right? And then the domain's in the middle and on the right is favors pulmonary hypertension therapy. So I'll just look at the side where it favors PH therapy. So it's worsening symptoms due to pulmonary hypertension in underlying CTD patients. And that's an important distinction and something that requires a lot of knowledge and experience to kind of ferret out. Are their symptoms worsening because they've got worsening fibrotic lung disease, or is it worsening pulmonary hypertension? So you would favor PH therapy if you think their worsening symptoms are due to PH.

And right heart cath, if their PVR is greater than or equal to 4 Wood units and the mean PA is greater than or equal to 25, that favors PH therapy versus someone who has a PVR of 2 to 3 and mean PA of 20 to 25, maybe they don't need PH therapy. Functional domain, it is talking about the pulmonary function testing. So if they have a mild or moderate restrictive defect, but they're limited by pulmonary vascular disease, the pulmonary hypertension is causing their limitations, that favors treating with PH therapy.

And then the biological domain is the NT-ProBNP and the BNP. If they're elevated, falls over into the favoring treatment with PH meds. And then if they have non-severe fibrotic lung disease on CT scan, also favors PH therapy versus somebody who has extensive ILD or has greater than 15% emphysema, then we may not treat those patients. And then other considerations just talk about drug interactions and reimbursement.

But I thought this was very nice to see something like this finally. Do you agree, Susie?

Dr. McDevitt:
I think it's very helpful. We have a database at our center, and it's always how do we label these patients who have both ILD and PAH and maybe a rheumatologic condition and the PVR is borderline? Is it Group 1 or is it Group 3 or? So I think things like this are very helpful for us to think about the patients.

Dr. Kingman:
I agree. Okay. So we are going to move on now to the questions and answers, and I believe our moderator is going to come or maybe we just read them. Sorry, I can't remember. Okay. So we have a question. How about I read it and, Susie, you can answer it, hopefully. I'm sure you can.

From a social perspective, was her child investigated for fetal alcohol syndrome disorder and ASD? Her child may need lifelong social support if there was fetal brain damage.

Have you experienced any difficulties with insurance reimbursement for dual-energy CT scans?

That sounds like your question, Suzy.

Dr. McDevitt:
Sure. I think these are both from case 2. They were asking about the 2-year-old child, was that child investigated for fetal alcohol spectrum disorders. And we had no contact with the child. So she came transferred to our hospital without the child. She had a friend watching her 2-year-old at home while she was admitted.

And we still haven't met her child, actually. She came back by herself for her follow-up visit. So she does have care there. She has a case manager, all of that, and care for her child. So very, very good question, but certainly, could be a lot of lifelong concern there.

And in terms of the dual-energy CT scans, we tend to use those. So you all know what I'm talking about. When you have a VQ scan that's tricky, the patient has parenchymal lung disease, the patient has had radiation to lung for some type of cancer, you can get some funky readings on CTPEs and VQ scans, and those are the times that we tend to do a DECT. We have one radiologist who reads those for us. A very, very expert eye in reading those. So we just do those on a case-by-case basis. We don't use that diffusely. We don't need that diffusely. But we have not had issues getting reimbursement on those case-by-case basis times that we need the DECT.

Dr. Kingman:
Okay. Thank you very much for that. We have another question. Can you speak about volume optimization? What is the best practice in your experience?

And I can just start on this in that first of all, volume management, I used to say, was what I do 90% of my time in clinic because most of the patients will have some degree of RV dysfunction and struggle with volume overload and really maintaining euvolemia is critical and something that we work on all the time with patients. We will generally use a loop diuretic as the beginning diuretic, Lasix usually, furosemide, and then adjust that as needed depending on how much swelling, weight gain, that they have. We have a whole program where patients monitor their weight every day when they wake with no clothes on, after they've used the restroom, and then they contact us if their weight is up 2 or 3 pounds in a week or overnight. And then we make adjustments and do repeat blood work afterwards to make sure they're creatinine is okay and their electrolytes. And I think that's pretty standard how we monitor. And then sometimes patients will have an elevated creatinine or they're really volume overloaded, and we have to admit them to the hospital, which is the most common reason for admitting our patients is for volume overload. And then we'll use IV diuretics and sometimes dopamine, too, as well, for blood pressure control or support. And low-sodium diet, of course. And we recommend patients don't drink over 2 liters of fluid a day.

Anything else you can add to that, Susie? It's pretty big question.

Dr. McDevitt:
The only other thing I would say, just because I spend so much of my time in the hospital and they're kind of often coming so sick to us, we're always very careful in a brand-new patient with a very large right ventricle and a very small left ventricle not to over diurese. So that, I think, is one other key point. When you have a new patient, over-diuresis is really a high-risk thing to do. That LV is already small and you're going to decrease their cardiac output. So when they're super sick and super early, and that's kind of what you hear about in the hospital, the teams don't want to over-diurese when a patient's pre-syncopal or syncopal and has a small LV. It's tricky. That that euvolemia is a little trickier in that case. Once they're treated and managed, yes, we want them euvolemic and we talk about how we fight with our nephrologists, the heart wants no fluid and the kidneys want the fluid, and so, yes, I think all your points are well taken.

Dr. Kingman:
And as you alluded to during your case, too, really important point is not taking the patient that has a lot of extra fluid on board to right heart cath. You really want to get the fluid off first so you have more accurate measurements.

Okay. We have 2 more questions. The first one is what change in practice pattern helped you the most with early diagnosis of pulmonary hypertension?

I guess the only thing that comes to my mind would be that when the mean pulmonary artery pressure and PVR were lowered, and how we define pulmonary arterial hypertension, that made us think about treating patients a little bit earlier, especially the patients that have connective tissue disease, we worry the most about those. I don't know what other change in practice pattern helped with early diagnosis. DETECT algorithm, as you talked about, Susie. Certainly, getting patients over to us quicker with that is done. Usually, at our practice, it was done in rheumatology.

Dr. McDevitt:
Yeah, I was going to say I think you're in your own centers, having kind of very collaborative working relationships with your GI, hepatology, your HIV, your infectious disease, all of those teams so they can be referring early. The ILD groups, making sure they're working with the PH group, because we find much earlier disease because now, we have awareness among all the providers. So that can be helpful.

Dr. Kingman:
Yes. And having treprostinil helped get everyone educated about PH ILD.

Okay, we only have 1 minute left and, Susie, this is a good question for you because I know that you're really good about this. And that is what role does genetic testing play in understanding and managing pulmonary hypertension, and how do you facilitate genetic testing in your practice?

Dr. McDevitt:
Sure. And you chime in, Martha, but since we only have a minute, we really try to refer all brand-new Group 1 idiopathic patients for genetic counseling. So you start with wonderful, educated genetic counselors and you do that referral and then move to genetic testing. Anybody that we think has suspected heritable, of course, we would also offer that, but all of the idiopathics and, also, those with suspected PVOD, we are discussing and, with shared decision-making, talking about genetic counseling. And we are fortunate to have a team of very educated and excellent genetic counselors at our center. So.

Dr. Kingman:
Great. Thank you.

Dr. McDevitt:
It's now covered by insurance. We help them with screening family members and all of those important things.

Dr. Kingman:
Yeah. The insurance is a big plus because back in the day it wasn't, and people had to decide whether they wanted to spend $2,000, it seems like, was the cost to go through that.

Okay. So, everyone, don't forget to complete your evaluation. It'll be emailed to you very shortly, and we thank you very much for your participation and attention during the program today, and hopefully it was beneficial for you. And we'll see you next time. Thank you.

Dr. McDevitt:
Thanks.

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