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Updates From the 7th World Symposium Task Force

Announcer:
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Episode 1: Patient Perspectives in Pulmonary Hypertension

Dr. Ford:
This is CME on ReachMD, and I’m Dr. Jimmy Ford from the University of North Carolina. We’re here to discuss topics recently reviewed at the 7th World Symposium of Pulmonary Hypertension held in Barcelona at the end of June of this year. The topic of today’s discussion is the patient perspective in pulmonary hypertension.

I am joined by Dr. Hilary DuBrock, associate professor of medicine at the Mayo Clinic. She’s an expert in patient-reported outcome measures and health disparities in pulmonary hypertension. I’m also joined by Gergely Meszaros, patient advocate and project manager of the European Reference Center, ERN-LUNG, who has been in the patient advocacy space in pulmonary hypertension for quite some time.

The field of pulmonary hypertension has evolved tremendously over the past three decades with the advent of multiple therapies, which have been approved, thus improving patients’ course and outcomes. However, disease and treatment burdens still weigh heavily on patients and much work is still to be done to improve the patient experience and their outcomes.

The World Symposium of Pulmonary Hypertension, held generally every 5 years since 1998, has highlighted relevant areas of PH, but only recently, at the 6th World Symposium of Pulmonary Hypertension in 2018, was the patient perspective addressed with a dedicated task force. The recent World Symposium in Barcelona built upon this to further explore the area and provide a framework for how patients

may live better with PH and meet their treatment goals. A summary of the proceedings with recommendations from this task force was recently published. Gergely and I served on this task force, and Dr. DuBrock was in attendance at the World Symposium as well.

So let me start with you, Dr. DuBrock. As an expert in this space, can you please share your impressions of the main areas of focus of this patient perspectives task force?

Dr. DuBrock:
Thank you for having me here today. I think the task force really addressed a lot of issues related to pulmonary hypertension from the patient perspective. They addressed, I think, varied global challenges in the diagnosis and management and treatment of pulmonary hypertension, and they explored issues related to things like social determinants of health and socioeconomic status that can impact access to diagnostic testing for pulmonary hypertension but also to our treatments and medications for pulmonary hypertension.

They also highlighted the need for better understanding of these global patient challenges and presented some data from a survey that they've done of both patients and providers across the world. And then they emphasized the importance of capturing patient perspectives and guideline development, clinical trial design, research, education, and advocacy efforts. And the overall theme, I think, was that the patient should really be at the center of everything we do related to pulmonary hypertension.

Dr. Ford:
Yes, and one other thing that really came to the forefront, amongst all of those other topics which you mentioned, was the use of patient-reported outcome measures as a sort of a central tool in really gathering the patient's unique perspective and individualizing how each patient perceives and deals with the course of having pulmonary hypertension. And we know that a number of these have been developed over the years, but their routine use is not very uniform. And I was curious what you, as a practicing pulmonary hypertension clinician, what do you see as some of the challenges to the routine use of patient-reported outcome measures, or PROMs, as we typically call them?

Dr. DuBrock:
I think the task force really highlighted the importance of PROMs in both clinical care and in the research setting and to help kind of guide patient care, but I think there are challenges to using them in a routine clinical setting. And the main barriers are typically time and that we feel like we don't have enough time to capture these PROMs from patients when we're seeing them in clinic. And then also maybe a perception that they might not be valuable in patient care.

And so ways to overcome those barriers, I think, are education, which is, I think, one of the roles of the task force, is really to educate PH clinicians and healthcare professionals of the value of PROMs and to make recommendations about the use of PROMs in clinical care, but then also finding ways to make PROMs more routine and that you incorporate them into our electronic health record and our daily management of pulmonary hypertension patients just to make it more convenient and easier as well.

Dr. Ford:
Right. So a lot of the barriers are really perceived by the provider, maybe not so much by the patient. And along those lines, Gergely, having worked in patient advocacy, particularly in pulmonary hypertension and lung diseases for quite some time, you've certainly been involved in some of the discussions about PROMs. And I was curious what your view is of what the patient's view is on the use of PROMs and how they might really serve to help empower the patient a bit more and sort of take more ownership of their care and have a more shared decision-making with their provider.

Dr. Meszaros:
As you might know it was the very first time that the European guidelines referred to the PROs and stating that it may be utilized and recommended. So the task force regarding patient perspective thought that it might be worth having a closer look how it is used in clinical practice. It is very well established, as we heard, in the clinical trials, but from patient perspective we understand that this variable tool is little bit underused in the clinical practice.

However, we believe that it's a very nice self-reflection tool and helps improve our patients. I also need to refer back to the proceedings and to the European Guidelines, which emphasize the importance of shared decision-making. PROMs are very useful to foster such kind of collaboration and cooperation and communication within healthcare professionals and patients. On top of that, it's a very nice complement to other clinical information, and with that it, can improve clinical management.

Dr. Ford:
Hilary, let me come back to you. So there are, as I mentioned, a few different PROMs available for use, some of them being pulmonary hypertension specific, and I think that's really what the focus was of the task force is really trying to parse out if there should be any preference given to one of the tools versus another. But I thought maybe if you could just provide us a bit of a brief overview of some of the relevant differences between them

Dr. DuBrock:
So there are really several different PH or disease-specific PROMs, that we use in clinical care and in research settings. And generally, what they do is they assess the symptoms of pulmonary hypertension such as dyspnea. They assess the effect of pulmonary hypertension on individuals' health-related quality of life, and their overall daily living and activity. Some, just to focus on few different examples such as emPHasis-10 and CAMPHOR have been validated and pretty well established for use in clinical care in pulmonary hypertension. But they vary in terms of the length and the time needed to complete those PROMs. So, for example, CAMPHOR is 65 questions, so fairly lengthy to complete for patients, whereas the emPHasis-10 is pretty short at just 10 questions.

So obviously, with more extensive questionnaires, you get more information about health-related quality of life and patient-reported outcomes, but there's a trade-off of having to take more time to complete to maybe being less practical in a routine clinic visit, for

example. There's a newer PROM, the PAH-SYMPACT, which was designed to assess the symptoms that impacts the pulmonary hypertension. And that was developed in accordance with FDA guidelines for patient-reported outcome measures, and it's been used in clinical trials, but there's less evidence for its use in the clinical setting and kind of routine clinical care. And then that one also has some licensing fees that may limit generalizability of it but certainly can also be helpful.

Dr. Ford:
So I think really the parting line from the task force was a PROM should be strongly considered to be used in routine clinical care, not necessarily a specific one. As you mentioned, some are easier to use with regards to the amount of time required or the availability of electronic formats, which might better be integrated into the medical record. And we certainly don't know or don't have any evidence as to how frequently they should be administered, right? So there's still some research to be done, I think, as to how best to implement PROMs and what they might help clinicians to determine about patient's course in treatments.

Dr. DuBrock:
I think it's pretty evident that it's valuable and empowering patients and incorporating them into shared decision-making and making sure that their voice is heard when we're making decisions about treatment and following them over time.

Dr. Ford:
Absolutely. It helps to provide a systematic framework to make sure that we're capturing the patient's perspective and individualizing their care with every clinical encounter. That's absolutely a great point.

So I wanted to shift gears a bit. And one of the other big focuses of the task force was the presence and continued evolution in terms of the complexity and reach of patient associations, and also just the number of them globally, noting, of course, that there are certainly areas of the world that are very much lacking with regards to the availability of patient associations.

So, Gergely, I was hoping maybe you could give us a bit of commentary about how these patient associations have evolved and also about some of the ideas that were brought forth about how they might be more consistently structured and some guidelines about how they might be organized moving forward to provide some consistency to patients and some ways that patients can tell whether an association has been vetted to some extent and the information that's being provided by them is indeed accurate.

Dr. Meszaros:
Yeah, Jimmy. Actually, I am happy to echo what you mentioned that patient organizations are evolving since the '60s when they were established. However, as we explore within the task force, there are still wide spots within the world map. So they have very well established, very well advanced patient associations which are rendering various services. I'm going to cover them later. However, we see that some parts do not even have access to patient organizations, which I think it's a great pity, especially for rare diseases.

As we explore this situation, we also needed to focus on the European Guideline, which also recommended the collaboration between PH centers and patient organizations. And there's a big question mark from healthcare professionals about how a patient organization should be considered as one which I need to cooperate with.

And as Jimmy asked a couple of minutes ago, the task force elaborated a very nice list, a kind of recommendation for patient organizations, how they can be independent, reliable, how they can become real partners with all stakeholders, from pharmaceutical companies to healthcare professionals to decision-makers and policymakers. And this comes to the very point of the involvement of patient organizations from these decades. In the very beginning, it was kind of a tabled discussion. We would rather say peer-to-peer support, where patients were supporting each other and try to overcome not only the physical but the mental burdens which puts on the patient's shoulders lots of difficulties. However, the patient organizations realized that if they are approaching, in a structured way, other stakeholders, they can actually have the whole community, and the work, it is not only done on a patient level. So they started working on raising awareness campaigns, like the World Symposium, which is comprising more than 80 patient organizations all over the world. There are specific days, for instance, for CTEPH Day which is in November. And we are also collaborating with other rare diseases on the Rare Disease Day.

Naturally, these kind of activities are addressing the general public. However, we also realized that there is a kind of information gap on the level of family doctors, general practitioners, and also those healthcare professionals who are dealing with more prevalent respiratory diseases, so we try to also cover these lack and provide information in such situations. And once it comes to the provision of information, it's a big challenge for patient organizations because there's Dr. Google. We're always referring to Dr. Google, and many, many resources are available on the internet. However, we try to make sure that patient organizations are ranking in such kind of Google search so we can provide reliable and up-to-date information to the patients.

Naturally, on top of that, there are other activities which patient associations are rendering and might contribute to the multidisciplinary

team. We, from patient perspective, believe that the holistic approach of patients is utmost important. These topics might cover traveling or mobility issues and also nutrition and others.

On top of that, and most recently, I think that this is one of the most important activities of patient organizations: it's noticing the activities. There are both international and local level. International level, we saw lots of activities within Europe like the pharmaceutical legislation. The European have the space where patients are involved, and most recently, there are reimbursement-related questions, so they have technology assessments. There's a requirement from the EU that patients and patient advocates should be included as experts.

But on top of that, it might be some local activities as well. Most recently, for instance, there was a very nice corporation where patient organizations, healthcare professionals submitted an application to reimburse portable oxygen concentrators for some countries.

So in a nutshell, as you can see, there are many, many activities patient organizations are rendering, and I firmly believe that with this involvement, patient organizations are a very important and integrated part of the healthcare system.

Dr. Ford:
Great. Thank you, Gergely.

So I think it's clear that much has been done to try to improve patients' lives and outcomes in PH largely by increasing their voice, but more work still needs to be done, really, to do a better job and achieve more equitable access globally and really better fine-tune individualized treatment, which really requires the cooperation of multiple stakeholders.

But I'd like to thank you both, Hilary and Gergely, for joining me today to talk about this very important topic. And I hope that our session here has really given our listeners something to think about and take home to their treatment of their pulmonary hypertension patients. Thank you so much.

Dr. DuBrock:
Thank you.

Dr. Meszaros:
Thank you for having me.

Episode 2: Special Treatment Considerations in PH: Transplant and Critical Illness

Dr. Ford:
This is CME on ReachMD. I'm Dr. Jimmy Ford. Today's episode is on pulmonary hypertension due to lung disease with updates from the 7th World Symposium. Here with me today are Dr. Oksana Shlobin, as well as Dr. Lucilla Piccari. This discussion will focus largely on pulmonary hypertension associated with COPD or emphysema and pulmonary hypertension associated with interstitial lung disease, but we'll briefly touch on some other less common entities within this group as well.

I'd like to start off by asking you, Lucilla, to give your impressions of the current state of pulmonary hypertension in lung diseases. And what are some of the important considerations around this with regards to prevalence and outcomes?

Dr. Piccari:
The pulmonary hypertension definition has undergone many changes, as you know, and in the 7th World Symposium, we have now a definition of PH of over 20 mmHg in the mean pulmonary artery arterial pressure as well as precapillary pulmonary artery pressure of ≤15 mmHg and pulmonary vascular resistance of over 2 Wood units. And so this is the current definition as per the 7th World Symposium. And obviously, many of the studies that we have have actually been conducted with previous definitions, so it is a bit hard to translate those into the current definition, but still, we know with these limitations that pulmonary hypertension in lung disease is very prevalent. It is the second most common form of pulmonary hypertension, or a group of pulmonary hypertension, and it is quite prevalent in COPD and ILD as you mentioned, which are the 2 main diseases that occur in combination with PH. The prevalence has mostly been studied in pretransplant patients where it can be quite high. On average, it's around 39%, 40% of COPD patients and around 30% for ILD patients, although obviously it depends on the population and the way that it's being measured. The diagnosis relies on right heart catheterization, which is not always available, so there are many things that we don't know yet. This is the group of pulmonary hypertension that has the worst prognosis of all of the groups of pulmonary hypertension, so it is really important that we find more data and especially more treatment strategies for these patients.

Dr. Ford:
Let's pivot to specifically talking about pulmonary hypertension related to interstitial lung disease, and, Oksana, if you could maybe describe to us what are the outcomes of this particular entity and how we really approach these patients in considering the relative hemodynamic severity of pulmonary hypertension and the relative severity of the lung disease physiologically and on imaging. And

furthermore, what do we know about the treatment of PH-ILD?

Dr. Shlobin:
I want to follow up on something that Lucilla said, and that's the information that we have about prevalence of the disease. Most of the studies were done actually in a particular type of fibrotic interstitial lung disease, and that's IPF [idiopathic pulmonary fibrosis]. IPF is the most common fibrotic interstitial lung disease, but there are other entities, such as fibrotic NSIP [nonspecific interstitial pneumonia] and fibrotic chronic hypersensitivity pneumonitis, and then obviously a lot of patients with connective tissue diseases also develop interstitial lung diseases which may be fibrotic in their pathogenesis. But again, the world of interstitial lung diseases is very, very, very wide.

The second point is that most of the prevalent studies that we have done are based on the 6th World Symposium definition, and even pre that, sometimes, the data that we have cannot necessarily be generalized to patients under the current definition of PH. So we do suspect, however, that there are going to be more and more patients that we see, especially with the milder hemodynamics, because the parameters of mean PA pressure and PVR were lowered.

We do know that with patients with mild interstitial lung disease and with patients with more severe interstitial lung disease, presence of pulmonary hypertension portrays very, very poor prognosis, so it's independent of the severity of the interstitial lung disease, and even a milder degree of pulmonary hypertension is detrimental. And actually, if you compare ILD-PH into PD-PH, patients with ILD-PH have by far worse prognosis. We see that these patients walk shorter, their functional class in general is higher, they require more oxygen, they get hospitalized more, the burden on caregivers is higher, so it's definitely a complication of interstitial lung disease that can affect not only day-to-day living but we know affects mortality.

So I guess to answer your question about the recent treatments, we do have one medication that in the largest trial of idiopathic interstitial pneumonias and pulmonary hypertension, which was hemodynamically diagnosed with mean PA pressure of 25 and PVR more than 3, so one of the older definitions, and that's the trial of inhaled treprostinil, or INCREASE trial, was shown to be beneficial based on the primary endpoint of placebo-corrected difference in 6-minute walk distance and also secondary endpoints, which was disease progression as well as the biomarker of NT-proBNP.

There were a number of post hoc analyses that were done that strengthened the data, and I know we don't have time to get into them, but based on all of the data that has been published, the World Symposium task force on pulmonary hypertension with associated chronic lung diseases did offer guidelines for treatment that includes inhaled treprostinil where it's available, which is right now only the United States, in the treatment paradigm.

Dr. Ford:
Thank you. So we've certainly seen some advances, especially with regards to treatment, from the 6th to 7th World Symposium, but it no doubt remains a very challenging population.

Similarly, Lucilla, I wanted to ask you to weigh in on PH related to COPD, and with many of the same questions, recognizing, of course, that we don't have an approved therapy for this particular entity but that pursuit of one has been a longtime process and will probably continue to be so. But if you could speak again to the relative hemodynamic severity and the severity of the physiologic and imaging findings in this patient population, and if you wanted to touch a bit more on outcomes and prevalence as well.

Dr. Piccari:
Yes, thank you. So, effectively, I think one of the biggest problems with PH-COPD is that it's such a prevalent condition because COPD is a prevalent condition, although it is probably very underdiagnosed across the world, and PH within COPD is even more underdiagnosed. So there are potentially many, many patients out there who have pulmonary hypertension in association with COPD, and although it is true that the outcomes are not quite as dire as those that we see in ILD-PH, it is still quite a somber diagnosis when the pulmonary vasculature is also impaired as well as the airways. And so as you mentioned, there are effects on the functional exercise tolerance of the patients and on their probability of suffering an acute exacerbation, which has been proven to be likely even below the threshold of pulmonary hypertension, so even when the mean pulmonary artery pressure is slightly elevated but not quite reaching that level. These patients have a reduced quality of life for sure, and then we see that this is magnified a thousand times when the pulmonary hypertension is severe. So there is a smaller group – fortunately it's a rare situation – where they have severe pulmonary hypertension, and these patients are really hypoxemic, they are absolutely breathless, they can walk very short distances, and their outcomes are very, very dire.

So as you mentioned, the quest to look for a treatment for these patients has been long and so far a bit underwhelming. Recently, the PERFECT trial tried to evaluate inhaled treprostinil in this group of patients and unfortunately was not successful, so inhaled treprostinil is not to be considered for COPD-PH patients. There are earlier studies which were conducted about 20 years ago that looked at other prostanoids, such as iloprost, that were cautiously successful in smaller cohorts, so it wasn't a large randomized controlled trial. There is

also some indication that maybe phosphodiesterase-5 inhibitors might be beneficial, but these are all smaller studies, and so we really don't have, such as in the case of an INCREASE in ILD-PH, we don't have a large randomized controlled trial that has shown benefit to these patients. But we absolutely need to find something for them because their morbidity and mortality is very high.

Dr. Ford:
I mentioned within group 3 of pulmonary hypertension, there are some less common entities that we do see occasionally clinically. One that I'd like to point out, and that the task force touches on, is the concept of group 5 sarcoidosis, but also having a lot of potential parenchymal lung involvement and behaving clinically and physiologically much like a group 3 PH patient and how we might approach those patients, and if any promising treatment prospects are out there for that group of patients.

So, Oksana, would you like to comment on that?

Dr. Shlobin:
I like how you just said it's a group 5 disease, but within group 5 disease, there is a group 3 pulmonary hypertension, and that's actually how I approach patients with sarcoidosis and pulmonary hypertension. The first thing that you have to do, and sometimes it takes quite a while and sometimes it's a mixed bag, is to figure out what the predominant etiology is of the impairment, and patients with sarcoidosis can have diastolic dysfunction because they've been on steroids and they're overweight and so forth, so the comorbidities. They may have pulmonary vein constriction by lymph nodes or fibrosing mediastinitis, they may have the impingement of the pulmonary arterial vasculature by large lymph nodes, and then, of course, they can have, and most commonly actually, have parenchymal lung disease. And usually when you have pulmonary hypertension and when you see pulmonary hypertension in that patient population, these patients have fibrocystic sarcoid or stage 4 sarcoidosis radiographically. And then in those situations, again, there is nothing that has been studied on any particularly large scale. There was a small trial of riociguat, actually, that suggested that maybe there is a benefit to this group of patients, and there are a number of very small, usually investigator-initiated trials that are currently underway, but nothing unfortunately on the larger scales. But with patients like that, once you determined, for example, that really their parenchymal lung disease is of fibrosing type and they have significant pulmonary hypertension, it's a conversation between the physician and the patient, and sort of your approach to treatment is based on a very open discussion between a patient and a physician that there is no data, but based on the pathophysiology, we can attempt to try certain treatments in a very cautious manner.

Dr. Ford:
I would just like to ask both of you to wrap up. What do you see as sort of the biggest needs to move this field forward and help us to treat group 3 pulmonary hypertension patients better by the next World Symposium?

Dr. Piccari:
One of the first things that we need to take into account that we maybe have not quite so much yet is the patients' perspectives and how they actually live with this disease and what are their priorities for what should the treatment achieve, what are the goals, what are the management goals, and basically to take into account how this diagnosis changes their lives and what can we do to improve that. So, personally, I think that this is one of the most urgent things that we should do in the space of group 3.

Dr. Shlobin:
So another thing that I'd like to add to what Lucilla was just saying is that we really need to phenotype these patients better. Until recently, group 3 PH was this big thing with everyone mixed together, and if you look at the registry data, it contains patients with COPD and patients with ILD and CPFE, and even the outcomes were often reported for the entire group of patients instead of separating them. So it's not until recently that we really started to look at those groups of patients separately. So phenotyping patients is going to be very, very important because this is something that hopefully is going to give us real-time data to study them. The other thing that we really need to do is get high-quality radiologic data, which has been missing for most of the registries, to really understand which patients develop disease and how it affects the outcomes.

Dr. Ford:
Great. Thank you so much. Well, that's all we have time for today. I'd like to thank you both for your expertise and excellent input and viewpoints, and I'd like to thank our viewers as well.

Episode 3: Special Treatment Considerations in PH: Transplant and Critical Illness

Dr. Ford:
This is CME on ReachMD, and I'm Dr. Jimmy Ford from the University of North Carolina at Chapel Hill. Here with me today is Dr. Ioana Preston, associate professor of medicine at Tufts University in Boston. This is Episode 3, special treatment considerations in pulmonary hypertension, focusing on transplantation and critical illness.

The field of pulmonary hypertension has evolved considerably, particularly with regards to diagnosis and treatment advances and risk stratification approaches, and we now have multiple treatment options. However, despite this, some of our patients progress to the point of needing intensive care unit support with vasopressors, inotropics, or other mechanical forms of life support, and even lung transplantation.

The World Symposium on Pulmonary Hypertension have traditionally addressed these areas and have continued to do so in the most recent 7th World Symposium on Pulmonary Hypertension. And though the need for lung transplantation in pulmonary hypertension has decreased over the years due to an improved number and efficacy of therapeutics, there still is a need for it and a need to enhance the referral process, the selection process, and the perioperative course. And the task force on lung transplant and bridging support in pulmonary hypertension addressed these issues.

Ioana, can you give us a brief description of how the acutely decompensated PH patient may present, particularly one that may be in shock with signs of end-organ dysfunction, and maybe some of the relevant pathophysiology?

Dr. Preston:
I would categorize acutely ill PAH patients that require intensive care into 2 large categories. One are those patients in whom there's a precipitating factor: new arrhythmias, an infection, a thyroid storm, or any, external to the PAH system, insult that decompensates rapidly the pulmonary hypertension and the right ventricle, and that needs to be addressed quickly. The second category are those PAH patients in whom the disease progresses to the point that the RV is so decompensated and they go into shock because of the worsening of their PAH.

So I think we have to treat as a global system, and if you think about pathophysiology quickly, whether it's an inciting phenomenon or it's an intrinsic worsening of the disease, the right ventricle in the setting of worsening afterload or end, increasing preload, decompensates. It increases size, it pushes onto the left ventricle, so it affects the left ventricular function. So this circling of right ventricle failure that causes left ventricular failure and back to the right ventricular worsening function, is like a circling drain that decreases the cardiac output tissue perfusion to all organs and puts patients into rapidly worsening hemodynamics and shock, multisystem shock.

Dr. Ford:
Can you comment a bit about what the treatment approaches are, considering what the inciting causes may be, and in addition, what are some of the things that we monitor in these critically ill patients with regards to their hemodynamics, their end-organ dysfunction, and even potentially their pulmonary hemodynamics, specifically?

Dr. Preston:
Right. So I think if there's a precipitating factor, this needs to be addressed very quickly, on an urgent basis. So it's exactly like when you have patients who come in with an acute MI or with a stroke. You need to treat the underlying cause very quickly because you don't have time. For example, if a patient comes with arrythmia and you let them stay in unstable rhythm, very quickly the RV will decompensate, so you want to act on and treat the arrythmia properly and fast, because you don't have time. Infection and all other causes need to be really, really treated promptly. And have a low threshold for these patients with underlying PAH or PH to be monitored in an intensive care unit because of the risk of acute decompensation. On the other hand, if there's a patient who comes in with worsening PAH to the point that they need intensive care monitoring, the pulmonary antihypertensives need to be instituted really rapidly.

So these are the 2 ballparks of how to approach on an emergent basis. But really, we need to follow these patients really carefully as we institute treatment and to optimize their hemodynamics to control their right ventricular function and avoid worsening and hope for improvement in RV function. And because our patients with PAH, when they're decompensated for any cause, they typically come volume overloaded.

The current recommendations outline very nicely, in a table, in a figure, to institute diuretic therapy very promptly, and also, if diuretics are not effective, to combine diuretics with renal replacement therapy. But also, the focus is to preserve systemic blood pressure to avoid hypotension, to use pressors if they're necessary, to preserve tissue perfusion, and follow carefully all the typical ICU parameters such as kidney function, lactate, and so on. But also, focus on right ventricular function by echocardiography as well as hemodynamics by a Swan-Ganz catheter in more severe cases. And that can help the intensivist as well as the PH physician in collaboration how to manage the pressors, the ultrafiltration, the supportive medications, the pulmonary vasodilators all at once to provide the best care and support.

Dr. Ford:
Can you maybe comment a bit about what the task force describe with regards to mechanical circulatory support, particularly VA and VV ECMO, and what are some of the advantages and disadvantages surrounding those and how they might be approached as either a

recovery or a bridge to another endpoint?

Dr. Preston:
Right. Right, and if all medical therapy and supportive therapy does not give the desired outcomes, we do have the option of assist devices, such as ECMO. But we have to plan it very carefully, of who we use this type of devices, because we have to have a plan of what's going to happen next.

So, currently, the ECMO devices, the support devices such as ECMO are recommended for bridge to transplant, to lung transplant, so that has to be in patients who have a high likelihood to be transplanted. They are already listed for transplant or they're young, they don't have any other comorbidities, and they passed the first test for being listed for lung transplant. The second is bridge to recovery.

So if there's an intercurrent infection, and there's a high likelihood that if we buy time for that patient to respond to treatment and to give them time to heal the intercurrent problem such as the infection that we were talking about, then the ECMO is a good possibility. Very seldom we offer ECMO to palliative care. It's due to allocation of resources but also to the risk of using this kind of devices. These support devices are not devoid of risks, so we really have to put into perspective what's the goal for therapy when we use ECMO. And for ECMO for PH patients, specifically, it's the VA [veno-arterial] ECMO that can be used.

The VV [veno-venous] ECMO will not help because it will not help the right ventricle. So that is a very important aspect. Of course, the newer devices such as PA-to-LA ECMO, if you would, can be of consideration; however, these require sternotomy so, really, it's even a second step of selected patients who can benefit from this type of support device. The field is moving rapidly compared to 5-6 years ago. We've been using support therapies, device therapies for support, much more, so I think we will be able to offer to more patients in the future.

Lastly, I think what we've learned is the RV Impella is not a good option for support as a device for PH patients because it does not alleviate the work of the right ventricle against the high afterload, which is the diseased pulmonary vasculature.

Dr. Ford:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jimmy Ford. Dr. Ioana Preston and I are discussing special treatment considerations in pulmonary hypertension with lung transplantation and critical illness.

Could you talk to us a little bit about what specific types of transplant, whether it be double lung, heart-lung, single lung, are associated with better outcomes and are most indicated for patients with pulmonary arterial hypertension?

Dr. Preston:
So we've learned in the past that single lung transplantation is associated with very poor outcome in PAH patients. PAH and lung transplant is a very specific and special entity, because the type of parameters required for a patient to be listed for lung transplant are unlike any other lung disease. The outcomes are different, compared to other diseases, so it has to be special care for the patient who you think requires lung transplant evaluation. So first of all, the transplants that are available for PAH patients are double lung transplants in most cases, but in very severe cases, double lung-heart transplant can be considered.

So we can see how PAH patients are such a special entity in the lung transplant world. Physicians need to be aware of patients who are at high risk and think about sending them for evaluation earlier. Patients with heritable disease, patients with pulmonary veno-occlusive disease, patients who have scleroderma PAH, they're higher-risk patients. Their disease develops fast. Their right ventricle is much stiffer than the other PAH subcategories, and their systemic underlying disease of scleroderma that can affect the GI tract, especially the upper GI tract, can put them at a higher risk during the transplant and after transplant. So these patients should be sent for a transplant evaluation sooner rather than later.

Dr. Ford:
Can you talk a little bit about some of the unique features about how PAH patients' posttransplant courses typically go, particularly in the early immediate phase versus what are their longer-term prospects if they manage to avoid early complications?

Dr. Preston:
Right. So, again, post transplant, they're still a special entity because if you look at the outcomes, posttransplant PAH patients have a higher risk of complications and mortality compared to other intrinsic lung disorders, patients who undergo transplant. So there is a dip in survival immediately post transplant in PH patients compared to other diseases. And that's because once you remove the diseased lungs and you put new lungs that have normal pulmonary vasculature, the right ventricle becomes much smaller, but the flow that goes through the lung overwhelms the left atrium and the left ventricle that has not been seeing normal preload for many years.

So there is a risk for an intrinsic diastolic dysfunction that these patients can incur postoperatively that puts them into severe pulmonary edema and graft failure and demise. So we've learned that maybe in more severe cases, if patients don't undergo heart-lung transplant,

ECMO pre- and a few days postoperatively can alleviate the overburden on the left ventricle to have a seamless transition towards a normal minor circulation over days after the transplant. And that has been associated with good outcomes. Of course, the best care is in the centers that have expertise in both ECMO and transplant, and these patients can benefit from the expert centers in this situation. So if you want to send your patient to lung transplant, search a center that has expertise in PAH transplant.

Dr. Ford:
Great. It really is some fascinating physiology and challenging in the perioperative course. Well, thank you.

I just wanted to mention, also, the task force document made some forward-looking points about the needs for improving transplant access, expanding the donor pool, and even the remote possibility of xenotransplantation and other related technologies to accomplish the availability of organs to patients.

Dr. Preston:
Yes. And I think, especially in PH patients, because these patients live far from the center, so if there is a lung available, there is the risk that the timing from the call to the transplant is not enough, so I think the improvements in lung transplant and lung preservation for the transplant have improved the chances for our PAH patients. Now, xenotransplant, I'm glad you mentioned it. There has been tremendous information and research for the heart transplantation, but lung is a little bit more complicated because it's the only organ that's open to air and to nonsterile environments every day and every minute. So we have to learn much more about xenotransplantation when it comes to lungs.

Dr. Ford:
Absolutely. Well, thank you, our time is up. That's all we have time for today. Thank you, Ioana. Thank you to our listeners.

Episode 4: Special Treatment Considerations in PH: Pregnancy and Pediatrics

Dr. Ford:
This is CME on ReachMD. I'm Dr. Jimmy Ford. Here with me today are Drs. Ioana Preston, associate professor at Tufts University, and Dr. Eric Austin, associate professor of pediatrics at Vanderbilt University. Our topic today is special treatment considerations in pulmonary hypertension, particularly pregnancy and pediatrics, with updates from the 7th World Symposium on Pulmonary Hypertension.

Advancements in risk stratification have improved our abilities to discern what treatments patients need and prognosticate their clinical course. However, there remain areas with significantly less data and guidance, and a couple of those include pregnancy and pediatrics.

Let's start off with the topic of pregnancy, which has traditionally been considered to be associated with very high maternal mortality with no real nuance for tailored risk assessment or treatment plans. Recent outcome analyses, though, have shown that a promising turn has been occurring with the application of improved prognostication, monitoring, and individualization of treatment plans. And this really becomes relevant at the time of diagnosis with any woman of childbearing potential.

Ioana, could you please expand on this and talk to us about how you approach a woman of childbearing potential at the time of diagnosis and the topic of pregnancy in general?

Dr. Preston:
This field has evolved tremendously in the past 10 years, and more so in the past 5 years, since the previous World Symposium for Pulmonary Hypertension. Many reports have shown and stratified the risk of PAH patients who become pregnant and go on to deliver, so we have a much better understanding of who is at the highest risk and who is at the lower risk during pregnancy. And risk is, we're talking about risk of worsening pulmonary hypertension, risk on the fetus and the newborn, and risk of worsening pulmonary hypertension, not only during pregnancy and delivery, but also after.

So the current guidelines, as outlined on the 7th World Symposium Task Force for Pregnancy, mirror the recommendations that were drawn in 2022, late 2022 by the European Guidelines in which pregnancy is associated with increased risk compared to normal population. However, the discussion about pregnancy is not blank statement, this is contraindicated, but more so to have a multidisciplinary approach and to make the patient and the woman understand the risks of pregnancy in her particular type and severity of the disease.

Dr. Ford:
I was wondering, if you could describe how the task force arrived at, and what indeed were some of the recommendations and guidance that was gleaned from this analysis.

Dr. Preston:

Yes, so we reviewed all the literature available from the last task force, so from 2018 to current, and went deep into each paper to better understand the conditions reported, the outcomes, the severity of the illness, and the underlying support that is given by the center.

So there are several important aspects that we understood and we've drawn conclusions from. First of all, the type of pulmonary hypertension is very important. Patients with pulmonary hypertension who have very well-controlled disease, in whom the right ventricle is small, in whom the hemodynamics are closer to normal, and have shown stability over time, have the lowest risk when they become pregnant. Patients, on the other hand, with Eisenmenger syndrome, with severe suprasystemic pulmonary pressures, as well as patients in whom the PAH is not well controlled, and they have signs and symptoms of severe disease, are at the highest risk.

So the approach is to counsel the patient ahead of time and to discuss in a multidisciplinary team, both with the obstetricians, with the critical care physicians, with a PH specialist, and with the anesthesiologist, what are the risks of becoming pregnant, carrying the pregnancy, delivery, and postpartum care, as well as the health of the fetus and the newborn. So it has to be stratified.

We also learned from several reports that looked at the experience of certain centers, large centers, who analyzed their data on outcomes before and after a clear multidisciplinary approach to pregnant patient was instituted, and it showed tremendous improvement in outcomes, both for the mother and the child after a multidisciplinary approach was instituted in that particular center.

Dr. Ford:
Could you just give us a few brief takeaways about some of the specific recommendations about monitoring and individualization of treatment, particularly in the peri- and post-delivery period?

Dr. Preston:
Right. So it's very important to tailor the PH medications during pregnancy and avoid certain PH medications that can be harmful for the fetus, such as endothelin receptor antagonists, soluble guanylate cyclase stimulators, and prostacyclin receptor agonists. So the main treatment is with PDE5 inhibitors and prostacyclins. And the follow-up of the patients, especially in the third trimester, needs to be really very, very close, every 2 to 4 weeks. And we recommend a planned delivery 35, 36, 38 weeks of pregnancy, before the natural delivery happens so everything is in control and all the teams are prepared for the delivery. We also recommend a C-section to take away the surge and the stress during a vaginal delivery. There have been many reports that suggested the C-section controlled, elective C-section is associated with good outcomes.

And in more severe patients who end up becoming pregnant, maybe they were not diagnosed before pregnancy, but they just presented pregnant and with new PAH, these are at the highest risk. The ECMO team can be consulted and, in really severe cases, to cannulate the patient before delivery in order to help transition not only delivery, but postpartum next days-period, which are crucial during the fluid shift that is massive after delivery.

Dr. Ford:
And now let's switch gears a bit and talk about another evolving space, so that being the management of pediatric pulmonary hypertension. Now, Eric, I've cared for a few late adolescent patients with PAH, but we really want to lean on your expertise to talk us through the newest Pediatric Pulmonary Hypertension Task Force documents and some of the really complex nuances of pediatric pulmonary hypertension.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jimmy Ford. Our topic today is special treatment considerations in pulmonary hypertension, pregnancy and pediatrics.

Eric, recognizing that 30% to 50% of group 1 PAH in children is due to congenital heart disease, can you talk us through the task force recommendation about the classification of congenital heart disease in pediatric PH patients?

Dr. Austin:
I really appreciate the fact that the task force highlighted that 30% to 50% of children with group 1 actually have congenital heart disease, because we see so many different varieties, of course, but sometimes we hear more about the idiopathic and the heritable cases in terms of our management. And so the symposium did a really nice job with the task force of focusing us and helping to remind us of the different ways that we can think about congenital heart disease in the setting of pulmonary arterial hypertension. And they really took a step forward in helping us to think about different categorizations of congenital heart disease with some updates from our previous task force reports.

And in particular, what they highlight is a series of different classifications, including the first one being Eisenmenger syndrome, second one being a left-to-right shunt that can be correctable or may not be correctable. They then go on to highlight the importance of thinking about coincidental defects, and this in particular has to do with atrial septal defects, which really should not cause pulmonary arterial hypertension in the pediatric population of any significant amount at all. And they really highlight the notion that these should be thought

of as coincidental, rather than driving causative pulmonary arterial hypertension in childhood, at least.

There's a next classification known as corrected congenital heart disease, which, of course, as you can imagine, is individuals who had defects that have been corrected but then subsequently developed pulmonary arterial hypertension that is hemodynamically confirmed.

And finally, they add a new category, which really highlights an important – small but important component of our patient population, which is individuals who really did not have a prolonged irregularity shunt. They may have had a transient shunt that was repaired within a few weeks or not at all. And those people can be exemplified by, for example, transposition to the great arteries, which is repaired quite early in life. And those people typically do not have early-onset pulmonary arterial hypertension, but then can, later on in childhood, develop pulmonary arterial hypertension.

Dr. Ford:
I was also intrigued by the introduction of a newer risk stratification approach and tool that really relied a lot more on validated risk factors and less on just expert opinion. Could you describe what's new in this tool and how it's useful to be applied clinically?

Dr. Austin:
Yeah, this is an exciting development in our field, and really a hot topic still ongoing, truthfully, and with more study to be pursued. And as the task force members acknowledge in their document, we do now have growing data that in individual studies that have, when compounded over time and looked at one another, really suggests that WHO functional class TAPSE, or tricuspid annular plane systolic excursion, as you know, or NT-proBNP or even BNP, are really 3 variables that have been really quite well validated in different individual studies of pediatric patients with pulmonary hypertension, most typically pulmonary arterial hypertension. They were included previously but have been really reemphasized as important and validated components of a risk profile.

I'll stop and say there that the risk profiles that have been developed in the adult literature are more advanced than our pediatric colleagues have developed, but we're working hard to do that. And as you can imagine, we've incorporated many of the other features, or at least evaluated many of the other features in pediatric patients that, those of you who focus on adult care, have done over time so beautifully.

So there are additional features which have now been added to the score and highlighted. The way that's been done is, rather than have a high-risk and a low-risk score, the task force members decided to say you have a high risk and you may have a lower risk if you have features that are part of this risk score. And what they included in this risk score, in addition to the 3 variables that I mentioned previously, are really highlighting the importance of growth and its challenge among people who are pediatric diagnoses. And those who have worse growth often have a higher risk of problems. People who have progression of symptoms was included but emphasized more.

And then different features of imaging was really incorporated to a greater extent, and that includes both echocardiography, not only TAPSE, as I mentioned earlier, but other features, including right ventricular fractional area change, LVEI both in systole and diastole, and some other features that we had not previously aggressively seen in the task force recommendations.

Of course, hemodynamics remains very important, including not only whether you have an acute response to vasodilator therapy in the cath lab using the Sitbon criteria, but also a greater emphasis on SVO_2 as well as PVRI and even mean PA pressure to systolic mean pressure ratio.

And finally, the task force members included more novel imaging techniques for our field, which specifically I'm referring to cardiac MRI. And thinking about the way that cardiac MRI can really very detail support information about the function of the left ventricle in ways that perhaps the echocardiogram nor the invasive hemodynamics can support.

So all told, you see a new table included for the task force document, which highlights individuals who would be at higher risk or those at lower risk. But they also do a really nice job of saying, look, we need to study these as a whole and a unit. And many groups internationally are working on this topic and trying to study these and really validate a formal, comprehensive task force-driven risk score, which remains still to be done to fully implement it in our clinical care.

Dr. Ford:
Sure. Thanks, Eric. Yeah, it certainly was a very robust remake of the risk stratification approach.

To close us out, I just want to touch on the topic of treatment. So we note that formal agency approval for pediatric PAH are not available for all medications we have that have been developed for adult PAH. And the task force presented an updated treatment algorithm to try to provide some guidance. Can you explain briefly how this task force developed the algorithm and, really, what are some of the highlights and new features that are useful for pulmonary hypertension-treating pediatricians?

Dr. Austin:
I think you highlighted a key issue is that we don't have the robust nature of either European- or North American-approved drugs. So we use these drugs, oftentimes, off label, but not always. We have several drugs approved in the United States and Europe, but not all of them, and that's outlined nicely in the task force document. I won't get into that today.

But what we also have is a reliance on real-world evidence, because our algorithms for care rely on reports in the literature as well as our expert experience. And then we try to extrapolate, of course, what is being done for adult-focused care around the world. And so there are variations that you see in the task force document that are slightly different from the adult world, and that is in part because we just don't have the comprehensive randomized clinical trial data and subsequent follow-up that you all have in the adult literature. But we have made a lot of progress, and they do a really nice job in the task force document of highlighting this.

They have a fairly, what they call, a pragmatic treatment algorithm, which is very nicely articulated. They run through several features of it that I think are worth mentioning here, and I encourage people to go back and read the document. And the first is that we just talked about the risk score, and the fact that we have an evolving risk management approach. We don't have a definitive risk score with cutoffs like are in the adult world, where we think about how we escalate or deescalate therapy, but we are now incorporating individuals as we think about them as lower risk, as I mentioned before, or higher risk in our therapeutic approaches. And we'll see that in a second.

They also emphasize the general superiority, and this is a change that's much more emphasized this year compared to the previous task force, in mono versus dual therapy or multitherapy. And the notion that combination therapy, for many of our sicker patients at higher risk, based upon features of risk scoring, should be considered at the onset of diagnosis, rather than in a more graded approach.

And the third thing they mentioned that I think is important to highlight, is that much of the reports on which we have to rely on do emphasize idiopathic, inheritable cases with some congenital heart PH thrown in there, but we don't have the robust diversity of different pediatric subtypes, either in PAH specifically, or even across other precapillary conditions that may not be categorized as PH, but with which we treat PH-directed therapy in children that we have in adults.

So there is quite a bit of caveats that still remain when we approach our children, and so I think that's important to keep in mind.

Dr. Ford:
Absolutely. Thank you, Eric. And certainly, there's been a lot of progress in both of these areas, with more investigation needed in the future. We're out of time today, but I'd like to thank both of you for your expertise and participation, and our listeners as well. And we'll close the session. Thank you.

Episode 5: Pulmonary Hypertension and CTEPH: What Providers Need to Know

Dr. Ford:
Our topic for today is chronic thromboembolic pulmonary hypertension, what providers need to know. We'll be talking about updates from the most recent 7th World Symposium on Pulmonary Hypertension.

Chronic thromboembolic pulmonary hypertension has been recognized in every World Symposium of Pulmonary Hypertension in the modern era where these have occurred roughly every 5 years since 1998, with it being given its own dedicated task force in 2013 at the 5th World Symposium on Pulmonary Hypertension.

Now we have seen an evolution in the nomenclature of this disorder as well, with the recognition that chronic thromboembolic disease can exist with or without pulmonary hypertension with this more inclusive term, CTEPD or chronic thromboembolic pulmonary disease, which the most recent 7th World Symposium task force is named.

The majority of our discussion will focus on CTEPH, or chronic thromboembolic pulmonary hypertension, but I do want to reserve some time to discuss CTEPD without pulmonary hypertension and how we might approach that in light of the task force recommendations.

So, Gustavo, to start off with, can you please give us a brief overview of how often CTEPH occurs after an acute PE, as well as what are the main drivers, risk factors, types of vascular lesions that contribute to the development of the disease?

Dr. Heresi:
Yes. So chronic thromboembolic pulmonary disease with pulmonary hypertension, it's a rare but very serious complication of one or more episodes of acute pulmonary embolism. The most accurate estimates of the incidence of CTEPH after an acute PE tell us that around 2% to 3% of patients will go on and be diagnosed with CTEPH after an acute PE. Now the estimates are challenging due to a variety of factors, including the difficulties in the diagnosis and also the frequent occurrence of chronic pulmonary embolism mimicking an acute PE presentation, but a number for people to remember of 2% to 3% is very reasonable. Now, the risk factors for the development of CTEPH after an acute PE include things that make sense, like a large clot burden, recurrent episodes of PE, idiopathic PE or

unprovoked PE, and then some underlying medical conditions, such as, particularly, the antiphospholipid syndrome and, less commonly, things like a splenectomy or chronic inflammatory disorders.

Dr. Ford:
Thank you. From the task force, we see the persistence of V/Q scan as the preferred test for screening for CTEPH, and, of course, right heart catheterization as the definitive hemodynamic diagnostic tool. Beyond the V/Q or ventilation/perfusion scan, though, can you comment on the relative role of SPECT V/Q versus planar V/Q, and then furthermore, the relative roles of CT pulmonary angiography, invasive catheter-based pulmonary angiography, and even MRI in making an assessment about interventions?

Dr. Heresi:
Yes. So chronic thromboembolic pulmonary disease is unique in the group of pulmonary hypertensive or pulmonary vascular disorders because chest imaging – detailed, precise, and accurate chest imaging – is particularly important. As you pointed out, of course, the right heart catheterization remains key for assessment of the hemodynamics, but chest imaging is essential for an appropriate diagnosis. The task force, appropriately in my view, has guidelines that have been recently published as well, continue to emphasize that the ventilation/perfusion scan, or V/Q scan, is the screening test of choice, and the reason for this is quite simple actually. It's a matter of a binary decision-making. If the V/Q scan is normal, without significant mismatched perfusion defects, you can be fairly certain that you're not missing chronic thromboembolic pulmonary disease. On the other hand, if the V/Q scan is abnormal, more detailed imaging is necessary to arrive at the correct diagnosis. And this remains true even in the era of CAT scans replacing the V/Q scan as the test of choice for acute PE. For chronic PE, the V/Q scan remains the preferred screening test due to its simplicity of interpretation.

Now, if you add single-photon emission computed tomography, or SPECT, to that, yes, the studies have shown that sensitivity and a specificity is higher for both acute and chronic PE because it provides you with a 3-dimensional view of the pulmonary vasculature, and perfusion defects are simply easier to identify. In the COVID era, in fact, a lot of centers, us included, moved completely to a SPECT without the ventilation part, and the task force actually mentions this as well. You can get your way with just a perfusion scan without the ventilation part because if it's normal, again, CTEPH is excluded. So if you're able to do SPECT, yes, sensitivity will be higher.

Now, CAT scan is usually the next test – again, very, very important for the recognition of CTEPH lesions – however, the key here to remember is that the identification of CTEPH lesions on CAT scan requires particular experience and expertise, which is really not widespread. Many radiologists, and certainly pulmonologists, have not been trained and lack the expertise to recognize these chronic PE lesions on CAT scan, lesions that will give you a perfusion defect on a V/Q scan, hence circling back to the fact that the V/Q scan is the screening test of choice. But in expert views, in expert eyes, the CAT scan is an excellent test, and, in fact, very commonly, if the CAT scan shows us proximal disease, and by proximal I mean main, lower, or proximal segmental disease, we usually don't need any further imaging to arrive at the right diagnosis, which brings me to the conventional pulmonary angiography, or the invasive pulmonary angiogram, which remains an important tool in the diagnostic assessment but frequently is needed to determine more distal disease located in distal segmental and subsegmental vessels. It is also very important for balloon pulmonary angioplasty planning, and, of course, the right heart catheterization can be done at the same time as pulmonary angiography. One key point, though, to remember is that we never exclude CTEPH based on a CAT scan alone, and this is a common clinical scenario where the CAT scan read is negative for acute PE or even for chronic PE, yet when reviewed by expert eyes or when further assessed by conventional pulmonary angiography, CTEPH lesions are very apparent.

MRI is another option not very commonly utilized. I think at this point, V/Q, CT, and pulmonary angiography are enough for most patients, but occasionally we resort to MRI/MRA, for example, in cases where contrasts cannot be given, given allergic reactions and so forth.

Dr. Ford:
Great, thank you.

For those just tuning in, you're listening to CME on ReachMD, and I'm Dr. Jimmy Ford. Dr. Gustavo Heresi and I are discussing special treatment considerations in pulmonary hypertension, specifically chronic thromboembolic pulmonary hypertension.

Another concept I want to emphasize that has been a major one for this most recent World Symposium of Pulmonary Hypertension, as well as other expert bodies that have put out recommendations about evaluation and treatment of CTEPH, is the idea of the multidisciplinary team [MDT]. Now, from your own experience working in a chronic thromboembolic pulmonary hypertension center, can you comment on the value and importance of this, as well as who are some of the typical team members?

Dr. Heresi:
Yes. The multidisciplinary team approach for the evaluation and treatment of CTEPH is crucial, and the main reason is that a lot of the therapeutic decisions, for better or worse, remain very subjective, and we will talk about operability assessment and other therapeutic

decision-making processes that really require a lot of experience and expertise. At this juncture, we don't have objective data to identify which patient should proceed with one or the other therapeutic intervention. So in cases like that, a multidisciplinary approach is crucial because different people bring different perspectives to the table. An MDT for CTEPH requires, for sure, a pulmonary hypertension expert. It definitely requires a person with experience and expertise in pulmonary vascular radiology, so chest imaging for sure requires, ideally actually, at least 2 pulmonary endarterectomy surgeons, and interventional person that has experience and expertise in balloon pulmonary angioplasty. I think those are the crucial members, and certainly our team has that composition, and then occasionally you will bring different people for selected cases for specific questions, but those 4 main specialties, 4 main types of expertise, are crucial for the multidisciplinary team.

Dr. Ford:
Thank you. And looking at the CTEPH treatment algorithm from the task force document, it seems relatively simple. However, it is a bit deceiving, as these patients, as you well know, usually have a lot of nuanced considerations with respect to deciding between PTE, BPA, and/or medical treatment. Can you give us a sense of some of the unique patient cases or challenges or characteristics that may make it difficult to navigate the treatment algorithm?

Dr. Heresi:
Yes, I completely agree with you. I think the algorithm is really straightforward, and I like it a lot, but you are absolutely right; it's deceivingly simple. I think it's one of those situations where the algorithm is really solid and simple, but the decision-making and the application of that algorithm is actually excruciatingly

complicated, and the main reason is this. The treatment of choice is pulmonary endarterectomy for a majority of patients with CTEPH. If you can operate, you should operate that patient. However, identifying who's a good candidate for this complex operation is very, very difficult, and it basically boils down to 2 major decision-making points. The first one is do you have enough clot burden that accounts for the hemodynamic compromise and that is surgically accessible. That's what we would call technical operability. And the second aspect is, is the patient a surgical candidate, right? If the answer is yes to both questions, then that patient should proceed to pulmonary endarterectomy.

Now, answering those questions, particularly the first one, is highly dependent on availability of precise and reliable imaging and also on the experience and expertise of the particular CTEPH team. What might be operable for one center may be inoperable for the other, which is why prior iterations of these task force documents recommended a second opinion if a patient is deemed inoperable. The other aspect, of course, is that the algorithm and the treatment options have expanded. Luckily, we have now percutaneous catheter-based approaches in the form of balloon pulmonary angioplasty, and the armamentarium of medical therapy has expanded with at least one approved medication in the US and others in other countries.

So the challenge here is really to identify the best treatment option for the best candidate and also identify in those who may benefit from one or more of the available treatment modalities. And the last thing I would say about that is this is why it is really important to make these decisions in an expert center, right? Or at least refer the patient for an initial operability assessment to adjudicate that initial crucial component.

Dr. Ford:
Excellent, thank you. Now, the task force document certainly goes through each of the 3 main treatment modalities, PTE, BPA, and medical therapy, systematically, but I wanted to ask you, did you find anything strikingly new or different compared to the 6th World Symposium recommendations in these areas? And particularly, I'd like you to comment on this idea of multimodal treatment, particularly in reference to the RACE trial that was published between the 6th and 7th world symposia.

Dr. Heresi:
Yes. So I think that pulmonary endarterectomy, PEA or PTE as it's referred in the US, remains the treatment of choice, and the task force outlines that very, very carefully and nicely. Not a lot has changed in the recommendation since the last World Symposium. With regards to balloon pulmonary angioplasty, what has changed is the body of evidence that supports its use in terms of safety and efficacy. I think over the last 5 years, registry data and clinical experience have taught us that balloon pulmonary angioplasty is actually fairly effective, and, in fact, in registry data for inoperable cases treated with balloon pulmonary angioplasty and medical therapy, survival is approaching survivals that are observed after pulmonary endarterectomy, in the low 90% at 3 years. So I don't think there is any debate at this point that BPA is an amazing treatment addition over the last 10 years or so, and the body of literature and the experience now, I think, support even more strongly the use of BPA, again, for cases who are deemed inoperable or for cases that have residual pulmonary hypertension after endarterectomy, which already starts giving you a hint of multimodality therapy, right?

So we now know that residual pulmonary hypertension actually is relatively common even after successful endarterectomy, 25%, up to

50% in some studies. So at least a quarter of cases after a successful endarterectomy are left with residual pulmonary hypertension. Until the availability of BPA, medical therapy was key to help those patients further, as well as those who cannot be operated. The reason for this is that medical therapy targets the microscopic vasculopathy that is present to one extent or the other in every CTEPH patient, but now we also know that in those with inoperable CTEPH, particularly those who have significant pulmonary hypertension as defined by a pulmonary vascular resistance >4 Wood units, and this is data from the RACE trial that you were alluding to early, we now know based on this study that if we treat those inoperable CTEPH patients with medical therapy in the form of riociguat prior to proceeding with BPA, the hemodynamic benefits are excellent, but the safety profile of BPA is better. In other words, there are less complications related to BPA in those patients who are pretreated with medical therapy in the form of riociguat.

So you can imagine nowadays, in 2024 after the 7th World Symposium, the journey of a CTEPH patient can include careful operability assessment, undergo a pulmonary endarterectomy, careful follow-up and monitoring to detect residual pulmonary hypertension. If that is present, careful assessment for residual disease in the form of clot, and if the PVR is >4, medical therapy with riociguat followed by balloon pulmonary angioplasty for the residual clots, and that will lead you to the best outcome in a patient that now is treated with 3 treatment modalities, including 2 mechanical interventions and medical therapy. Now, not everybody requires these. We still see patients that respond very well after endarterectomy and that's all they need, but I think the key point here is even after successful surgery, look for residual PH and know that you can improve those patients further with BPA and medical therapy.

Dr. Ford:
Thanks, Gustavo. Before we wrap up, I'd like to ask you one more question about an area that remains a real challenge, and that is chronic thromboembolic pulmonary disease without pulmonary hypertension. Now, this was not tackled in significant detail in the task force document, but I was wondering if you could give us a brief synopsis of how you approach these patients and what diagnostic testing may be helpful in determining if a specific treatment, such as PTE or BPA, may be of benefit.

Dr. Heresi:
Yes, this is a challenging group of patients, and we do know that that syndrome is a bit more frequent than CTEPH after an acute PE. I told you earlier at the beginning of our conversation, 2% to 3% incidence of CTEPH after acute PE. The German FOCUS study showed us that for CTEPH potentially can be as high as 16%, although that estimate includes people with a so-called post-PE syndrome, but at least an early hint that some of these cases may be more frequent than overt CTEPH. We also now know that, luckily, the natural history of this entity of chronic thromboembolic pulmonary disease without resting pulmonary hypertension, it's actually rather benign. We have now reasonable amount of patients that have been followed for a few years, and rarely these patients go on and progress to resting pulmonary hypertension, and very rarely these patients die with cardiopulmonary failure, so the natural history in that regard is actually rather benign. However, some of these patients are indeed quite symptomatic and functionally limited by chronic thromboembolic pulmonary disease. The way to find those patients, the way to tease that out, is to do careful exercise testing, and in expert centers, we do invasive cardiopulmonary exercise testing, meaning our traditional cardiopulmonary exercise test with the addition of a right heart catheterization where we can measure the cardiopulmonary physiology carefully, not only at rest but also with

exertion. If we see there the footprint of chronic thromboembolic disease leading to pulmonary vascular limitation in the form of exercise-induced pulmonary hypertension with right ventricular dysfunction and/or ventilatory inefficiency, the patient is probably symptomatic or limited by the chronic clots. And in very selected cases, pulmonary endarterectomy or balloon pulmonary angioplasty can be used, and we have seen many cases where these mechanical interventions actually do lead to significant improvements in patients' symptoms and quality of life. So that's how we think about this entity, but it certainly requires very, very careful assessment and a lot of thoughtful decision-making together with the patient, of course.

Dr. Ford:
Excellent. That was very enlightening. Thank you. Well, that's all we have time for today. Gustavo, I'd like to thank you, and I'd like to thank our listeners.

Dr. Heresi:
Thank you so much for having me. It was my pleasure.

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