ISSN 1933-088X

Advances in Pulmonary Hypertension

Vol 18, No 3; 2019

Official Journal of the Pulmonary Hypertension Association

Behind the Scenes at the World Symposium on Pulmonary Hypertension 2018

Hemodynamic Definitions and Updated Classification—Impact on Clinical Practice: A Conversation With Erika Berman Rosenzweig and Nicholas Hill
Erika Berman Rosenzweig, MD; Nicholas Hill, MD

Risk Stratification—What's My Risk? A Practitioner's Tool
Ioana R. Preston, MD

Pulmonary Hypertension Due to Left Heart Disease—Combine or Not Combined? DPG In or Out? A Practical Approach to the Patient With Suspected Left Heart Disease
Thenappan Thenappan, MD

Pediatric Pulmonary Hypertension on the World Stage: Do We Need Separate Neonatal Guidelines?
Steven H. Abman, MD; Csaba Galambos, MD, PhD

Pulmonary Hypertension Roundtable: Behind the Scenes at the World Symposium on PH 2018
Erika Berman Rosenzweig, MD; Vallerie McLaughlin, MD; Greg Elliott, MD; Robert Frantz, MD; Nicholas Hill, MD

PH Professional Network: Bridging the Gap: A Multidisciplinary Approach to Transitions of Care
Susanne McDevitt, MSN, ACNP-BC; Claire Walter, PharmD, BCPS

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

Advances in
Pulmonary Hypertension
Official Journal of the Pulmonary Hypertension Association

PUBLISHER
Pulmonary Hypertension Association
Brad A. Wong, President and CEO

PHA OFFICE
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PUBLISHING OPERATIONS
Clarissa Nemeth,
Managing Editor
Allen Press, Inc.

Advances in Pulmonary Hypertension is available online at www.AdvancesinPH.org.

Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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*Advances in Pulmonary Hypertensio*n is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

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- A unique user profile that will allow you to manage your current subscriptions (including online access)
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Congratulations to Erika Berman Rosenzweig, MD, the Guest Editor for this issue of *Advances in Pulmonary Hypertension* (PH). Dr Berman Rosenzweig created an exceptional expert-driven "behind the scenes" discussion of the 6th World Symposium on Pulmonary Hypertension (WSPH), which convened in Nice, France, in February 2018. This is an invaluable resource with sections authored by WSPH task force leaders and experts.

In the first section of the issue, Dr Berman Rosenzweig is joined by Dr Nicholas Hill for an important dialogue regarding the updated hemodynamic definition and classifications. They discuss how these changes that were proposed during the meeting will affect clinical practice. They discuss not only how and why these changes were proposed, but also how we as the PH community can implement them into our daily practice. This discussion brings two of the world's experts together to reflect on two of the most important topics at the WSPH meeting.

Risk assessment and stratification of our patients was a major focus at the WSPH. Dr Ioana Preston details the strong relationship between stratification and outcomes. Dr Preston eloquently discusses each risk assessment tool and compares and contrasts them in order to point out the benefits of each for our patient assessment.

Dr Thenappan Thenappan authored the section on the practical approach to evaluating and managing PH due to left heart disease (Group 2 PH). He discusses the pathophysiology of Group 2 PH as well as defines and analyzes those patients with combined precapillary and post capillary PH (CpcPH). This section provides an excellent literature review on both subjects.

Dr Steven Abman and Dr Csaba Galambos thoroughly detail the challenges addressed at the WSPH on the pediatric PH population. In their article, they reflect on the issues of pathobiology, assessment, management, and outcomes of the pediatric diseases associated with PH.

Susanne McDevitt , MSN, ACNP-BC tackled a very important topic for our PH patients in the PH Professional Network (PHPN) section. Ms McDevitt discussed the complex process that occurs for our patients when they are transitioning from the hospital to home. This process needs to include a multidisciplinary approach to make sure that everything that a patient will require at home is available.

Last, but definitely not least, was the "Round Table of Champions." This world-expert led discussion focused on some of the most challenging and controversial issues presented at the WSPH. Drs Berman Rosenzweig, Vallerie McLaughlin, Greg Elliott, Robert Frantz, and Nicholas Hill discussed the proposed hemodynamic changes, as well as some of the changes in the classification system. The welcome addition of a patient perspective to the WSPH was detailed as well. A special thank you to Dr McLaughlin, who described the establishment of the newly created association of the WSPH, called the WSPHA.

This outstanding issue of *Advances*, which covers the 6th WSPH meeting, is a vital resource for all of those in our field. The authors provide their reflections of this important meeting in each of their sections. We will all learn so much from each of their articles.

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GUEST EDITOR'S MEMO

As guest editor for *Advances in Pulmonary Hypertension* this quarter, I had the great opportunity to work with some key experts in the field of pulmonary hypertension (PH) to highlight the 6th World Symposium on PH meeting (WSPH; 2018, Nice, France). In this *Advances* issue, we have captured some of the most important discussions that have followed the WSPH meeting, including an outstanding roundtable discussion with some leading PH experts who participated in the meeting. I believe this issue is timely, as it has given us a chance to digest some of the updates and enabled us to incorporate the discussions that have ensued since the most recent WSPH meeting. I also want to commend the organizers of this WSPH meeting, who incorporated a task force focused on patients' perspectives for the very first time. Pulmonary Hypertension Association (PHA) president and CEO, Brad A. Wong, was included as a task force member, giving the PHA a strong international voice. This is particularly meaningful to the PH community that PHA serves, and is a noteworthy addition to the WSPH symposium.

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Hemodynamic Definitions and Updated Classification—Impact on Clinical Practice: A Conversation With Erika Berman Rosenzweig and Nicholas Hill

In this special discussion for PHA, Guest Editor Erika Berman Rosenzweig, MD, sat down with Nicholas Hill, MD, Chief of the Pulmonary, Critical Care and Sleep Division and Professor of Medicine at Tufts University School of Medicine, to cover hemodynamic definitions, updated classification, and implications for clinical practice.

Dr Berman Rosenzweig: As you know, this is part of the *Advances in Pulmonary Hypertension* issue which is a behind-the-scenes look at the World Symposium on Pulmonary Hypertension (WSPH) 2018. We're lucky to have you here to discuss the issues that were raised in the proceedings on hemodynamics, updates and definitions, and the WSPH classification system.

First of all, Nick, thank you for joining us today

Dr Hill: It's my pleasure, Erika.

Dr Berman Rosenzweig: Why don't we kick off with some of the most lively discussions we heard at the symposium—one of which focused on the discussions around proposing a new hemodynamic definition of pulmonary hypertension (PH)? It was suggested that the hemodynamic definition of PH change from a pulmonary arterial (PA) pressure ≥ 25 mm Hg to > 20 mm Hg. I wanted to get your thoughts on that and how you think it might impact the field going forward.

Dr Hill: Well, I did give a presentation at the American Thoracic Society annual meeting in May and I gave some background and also raised some of the issues surrounding this. As I'm sure most people in the field know, this is something that had been percolating for a while. Just by way of very brief background, the ≥ 25 definition dates back to the first World Health Organization meeting of the world symposium back in 1973. At that time, they made some quite prescient observations.

One being that it's unusual to see mean PA pressures over 15 mm Hg in a normal population, so that over 20 mm Hg is really abnormal. They admittedly, at the time, somewhat arbitrarily chose 25 mm Hg or above for a couple of reasons. One being that they were concerned there might be overdiagnosis and overtreatment with a lower threshold.

At the next meeting of the World Symposium in 1998, the panel agreed that 25 mm Hg and over should stay as the definition. They also came up with this idea that if you increase your mean PA pressure over 30 mm Hg during exercise, that was "exercise-induced" PH, which was subsequently thrown out in 2008 when it became clearer that no one could agree on an exercise definition anymore. As people age, many have mean PA pressures that go over 30 who are otherwise normal. So that definition of exercise-induced PH has not been reinstituted.

In 2013, there was a fair amount of discussion about the fact that if you look at a large population of patients, as was done by Gábor Kovács in his analysis and published in *European Respiratory Journal* in 2009, where he looked at something like 50 studies dating back to 1947 on normals who had undergone right heart catheterization—there were over 1,100 patients—the overall average mean PA pressure was 14 mm Hg. The standard deviation was 3, meaning that 2 standard deviations get you up to 20 mm Hg. Therefore, greater than 20 mm Hg would be abnormal in a statistical sense. At the time, they talked about the 21- to 24-mm Hg group as a borderline range. That almost became an official designation, but the committee backed off from that and left it as more of a discussion point. More recently, in the 2018 meeting the committee re-examining the definition decided that there was enough evidence that had accrued to say that pressures between 21 to 24 mm Hg were abnormal and that they should be included as part of the PH definition.

The evidence they were talking about came from a number of studies that showed that if you have PA pressures between 21 and 24 mm Hg, although mean PA pressures of 21 to 24 mm Hg are associated with better outcomes than pressures of 25 or over, they aren't as good as pressures of 20 and below. Some scleroderma studies also showed that the people in this borderline range were more apt to develop PH over a period of years. Of course, the caveat is that this is all based on association and not causality. We don't really know what caused those deaths. Nonetheless, the decision was made to change the definition of PH to a mean PA pressure over 20 mm Hg.

Dr Berman Rosenzweig: I think that's a great background of how this has evolved over the years. The back and forth speaks to the fact that the evidence is not completely clear on what this proposed change in definition means and how it might impact the future of PH. For example, what does it mean for patients who, let's say, have a pressure in a lower range that may have been followed or evaluated for PH and not treated? Does it mean we can go forth and treat patients in that range now, even though our drug studies have not been focused on that group? What are your thoughts on that?

Dr Hill: Virtually all of our therapeutic trials to date have used the definition of 25 mm Hg or over for enrollment. We really don't know what the effect of treatment is on this previously referred

 DOI:10.21693/1933-088X-18.3.80

to as "borderline" group. I don't think we're going to get too many insurance companies jumping up and down enthusiastically about paying for therapy in this group either.

The definitions committee used the term, "We propose" this new definition. I have had insurers turn patients down who have borderline pressures and exercise-induced PH (with mean PA pressure >50 mm Hg during exercise) because of the lack of evidence to support therapy. I don't think they'll cover now just because the World Symposium has proposed a change in the definition. Unless we get some evidence, I don't think we're going to be able to use these drugs if we have to rely on getting insurance to cover in this borderline range.

Dr Berman Rosenzweig: Right. As you highlighted, this is just a proposed definition, but I do think it sends the PH community a call to action to start to study these patients and perhaps monitor them a little more closely.

Dr Hill: Absolutely.

Dr Berman Rosenzweig: Would you recommend following them more closely perhaps than we did in the past?

Dr Hill: Yes, absolutely. If I had been on the committee, I would have considered proposing a change, but would have designated the 21 to 24 mm Hg range an official "borderline PH" group and encouraged more study before proposing it as a new definition. Some of the prior studies have been based on echocardiographic findings. We need invasive hemodynamics and it would be reasonable to contemplate doing drug trials targeting these patients now.

Although I think if I were running a pharma company making PH drugs, I'd be reluctant to jump into this pool without careful forethought because the likelihood that they're going to respond like people with greater PH is low in my estimation. I think that because pressures in this "borderline" group aren't as high, it will take more patients over more time to show an effect, which means a lot of expense. Also, this is not a huge population in most PH registries.

Dr Berman Rosenzweig: I think those are excellent points. I think it does raise the question of how will we best study this group of patients if there may not be the commitment by industry to study them for those reasons you just stated. Perhaps we have to just look at prevention of disease progression, but that takes, as you said, a lot of patience and a lot of time to look at. It will be interesting to see how this pans out. What about with respect to other groups, non–Group 1? Is this affecting the other groups like chronic thromboembolic PH, for example?

Dr Hill: Yes. Well, I think I'd first like to bring up a problem I see with all of this that I raised at the symposium. That's what I refer to as the pulmonary vascular resistance (PVR) problem. When they made this proposal about the mean PA pressure, they also proposed that the PVR of 3 Wood units be retained.

The PVR of 3 had been tacked on to the definition in the past, that in addition to having a mean PA pressure over 24, 25 or over, the PVR, if you wanted to have PH, should be over 3 Wood units or 240 $dyn \cdot s^{-1} \cdot cm^{-5}$. We had accepted that, but it really applied only to the patients in Groups 1 and 4, but it had not previously been applied to Groups 2 or 3.

The committee in 2018 decided to retain the PVR of 3 for a couple of reasons. One, it had been established in previous World Symposia, and two, it had been used as a cutoff for eligibility in assessing patients for heart transplant or surgical repair of intracardiac shunts.

The problem is that the rationale for using the mean PA pressure of greater than 20 was based on statistics and epidemiology, which they considered as a scientific approach. Well, if they had taken the same approach to PVR, they would have come up with a very different number. It turns out that in Kovács' study, if you looked at the PVRs and all these normals, the overall mean was 70 dynes/s per cm^{-5} and the standard deviation was 30.

If you convert convert that to Wood units, the overall mean was 0.9 Wood unit. If you add 2 standard deviations to 0.9, you get 1.7 Wood units. That might have made more sense based on the same scientific rationale to select this cutoff rather than 3. If you select 3 as your cutoff, what you're doing is basically saying that either you have a very large transpulmonary gradient—thinking about how we calculate a PVR, the transpulmonary gradient divided by the cardiac output—or you had to have a very small cardiac output. There aren't a lot of patients whose mean PA pressures fall in the borderline range who meet these criteria. There was a pro/con debate on the new definition in the April 4, 2019 issue of the *European Respiratory Journal*. The authors making the Con argument surveyed PH patients at registries at their centers and could identify only 1%-2% of over 3000 patients who had mean PA pressures between 21 and 24 and met the PVR >3 definition. By applying this PVR, you basically don't have a population to study.

Dr Berman Rosenzweig: Obviously, that's a big issue if we really want to study this issue—who are we talking about exactly with the definition as it is? I guess if the PVR was not included, that would be different.

Dr Hill: Right. That would have been more sensible. Even if they had wanted to include PVR and had selected 1.7 based on the scientific rationale they used for PA pressure, it would include substantially more patients. I don't see why you would want to set a PVR limit on the "borderline" group because what you really want to do is cast a broad net to study the borderline group.

We could put a registry together to track them and get more rich data on them and then you learn more. It's worth mentioning that the Pulmonary Vascular Disease Phenomics (PVDOMICS) network to which we both belong decided to include a "comparator" group consisting of subjects who fit into different PH groups based on clinical criteria, but whose mean PA pressures were <25 mm Hg. These patients have been carefully phenotyped and are undergoing sophisticated omics analyses, and findings on this group, that contains mainly patients

with "borderline" pressures, should be very informative. In retrospect, it was fortuitous that we decided to retain this group.

Dr Berman Rosenzweig: Right. I think that will be fascinating to see how that shakes out, and certainly timely as well. Well, it sounds like this proposed definition, if you will, has raised as many questions as answers. I think it just opens the dialogue as you say to perhaps refine it, and figure out better ways to study these patients so that we know more in terms of what this all means with respect to outcomes.

Dr Hill: I think it's healthy to raise questions like this and generate a lot of discussion and controversy. It makes people think. A lot of people think and you get good creative thoughts. In the end, it will move the field forward, but it certainly needs to be refined. As I said before, I think it would have made more sense just to say, "Let's make this borderline category official and let's study it rather than redefine just yet."

Dr Berman Rosenzweig: Now, that's a great overview of the history of how this evolved and, hopefully, the future and how we can further study, learn, and maybe apply this proposed definition of PH. With that, I'm just going to shift to the second part of this conversation, which is yet another topic that I would say was a hot topic at the WSPH meetings and that always is, which is the update of the diagnostic group classification system for PH.

We know that's been a work in progress from the very beginning, when you either had primary or secondary PH. Now, we've got a 5-group classification system, which keeps getting tweaked. I was hoping we could talk about some of the changes from the most recent meeting. I guess the first one that I thought was very interesting, of course, is that there's now another specific subgroup under Group 1. That is for patients who are vasoreactive. That is a move that I'd like your opinion about in terms of what you think of this proposed change and that as a separate entity within Group 1 PH?

Dr Hill: Well, we've been aware of this group for a long time. Of course, we've routinely been doing vasoreactive testing. We also have the insurance companies who generally want us to sign off on some attestation that we've considered using calcium channel blockers first rather than move on to these much more expensive drugs.

It's been out there for a long time. It's a subgroup that we have sought ever since the work of Stuart Rich, MD, almost 20 years ago on calcium channel blockers. The Rich criteria defined it as a decrease in mean PA pressure and in PVR ≥20%. Of course, in 2005, Olivier Sitbon et al. came up with the definition we currently use for a positive acute vasodilator response, characterized by a drop in mean PA pressure by ≥10 mm Hg or ≥20%, reaching a mean PA pressure of <40 mm Hg and increased/unchanged cardiac output.

That predicted that about 50% of people meeting those criteria who were put on calcium channel blockers would manifest a long-term response. We all have a few of these patients in our practices. They do very well, a lot of them, in the long term. I think it's important to identify it as a separate subgroup because I think there are going to be characteristics of this subpopulation that will enlighten us if we study it as a separate subgroup.

Once again, I think the work of the PVDOMICS is relevant here because we also are interested in looking at this separately, as you know. I would predict that there are going to be genetic differences among these vasoreactive patients compared to nonvasoreactive and also probably other omic differences that will enable us to practice more precision medicine and have more effective targeted therapies for them.

Dr Berman Rosenzweig: Yes, I agree. I think this kind of robustly vasoreactive phenotype is almost a different disease entity. I also agree with putting it as a separate group. We have the opportunity to really hone in and learn a lot about these patients and why they respond the way they do. I'm kind of excited about that, that it's got its own designation. I guess in a similar vein because I often find, I don't know if you've had the same experience, that some folks—particularly the more junior folks—have never seen one of these patients in their practice. And even though someone's vasoreactive, they might not start a calcium channel blocker because somehow they think maybe one of the newer agents will be even more effective. I know you've seen robust responders. You said that, and I've had the same experience, they can go on for many years with calcium channel blockers alone.

Dr Hill: I had one of them die last year, but he had been on treatment for 40 years.

Dr Berman Rosenzweig: Wow, that's impressive.

Dr Hill: I have another calcium channel blocker responder who has been stable on CCB therapy for more than 20 years. She's a physician whom I met when she was in her residency and was having trouble keeping up with her friends climbing Rainier. That was kind of the canary in the mine experience where we picked her up early. She had moderate PAH initially, but has had normal estimated PASP by echo since starting calcium channel blockers and walks 700 m in 6 minutes.

That's the kind of response you really want. You don't see it all the time. Like I said, about half of the people who meet the definition for positive response have a favorable long-term response. I also think that we are going to rethink the definition because we not only have the calcium channel blocker responders, but we have superresponders to other drugs. I think each of these kinds of hyperresponders are of interest and are going to enlighten us about the pathophysiology of the disease.

Dr Berman Rosenzweig: That's a great point. There are these different phenotypes for drug responsiveness and probably the pathways. I think just having this as a separate group raises a lot of really interesting, good questions. I hope that we'll learn more from this group. I think we will.

Another change, which I thought was interesting, was the addition to—or I would say sort of a refinement in terms of how we look at patients with pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH). It really is a spectrum of disease with pulmonary arterial hypertension (PAH). There were good conversations about this especially now that we have an associated genetic mutation as a potential clinical marker and better imaging techniques. What are your thoughts in terms of that change?

Dr Hill: Well, I think we've been moving in this direction for a while because pathologists were the ones who first clued us in. It's hard to draw clear distinctions between those who are diagnosed with PVOD and the people who were diagnosed with PCH. A lot of these patients manifest features of both. Now that we have the *EIF2AK4* gene and it is occurring in both, I think it's much clearer that they really are different parts of the spectrum of the same condition. Anyway, I think we're just scratching the surface now. It was like the discovery of the BMPR2 receptor where we're just now starting to see treatments that are actually going after that mechanism entering the clinical space. I think we're now going to see a lot of work on what is the mechanism that links this gene with this pathology. I think it'll be very exciting to see this evolve.

Dr Berman Rosenzweig: Again, I think our radiologists have gotten better at imaging in terms of noninvasive ways to diagnose these patients as well. Nobody wants to do a lung biopsy for a patient with severe PH and potentially PVOD anymore. It is interesting because sometimes you'll treat a patient with what you think is PAH and then, obviously, they don't do well when you start titrating up your intravenous prostanoid. They might do well for a little while, a honeymoon period.

Dr Hill: I found that I'm really not very good at making a preclinical diagnosis of PVOD or PCH. Many patients don't manifest the typical features you read about in textbooks; what looks like left heart failure with septal lines with a normal-sized heart and with significant PH, but a lot of people don't manifest that.

We've all seen people who really don't have much on their CT scan imaging, who we would pass on having PVOD. And we see people who have nonspecific abnormalities but are behaving like they have PVOD in terms of getting into trouble when we start drugs. When we get the path eventually, it's not PVOD. I think having a genetic marker is going to help us a lot.

Dr Berman Rosenzweig: I agree. I think including leading to potentially new therapies?

Dr Hill: Yes.

Dr Berman Rosenzweig: Getting turnaround on a genetic marker is not always the quickest. If we can put it into clinical practice because the treatment pathways are so different where you might do early transplantation for these patients, I think that would be an amazing advance. I want to ask one final question because, again, I know the role that you have in the omics program—

Dr Hill: We could go on and talk about it for a long time. [chuckles]

Dr Berman Rosenzweig: Forever, I know. This is my last question. Maybe to put you on the spot a little bit. With regard to the classification system, there are these 5 groups. We're learning from our omics experience that not everybody fits nicely into one group. Can you maybe just speak for a minute about what we've observed in terms of mixed phenotypes and the complexity of what we're seeing?

Dr Hill: This, of course, is something we knew about. Your work along with Evelyn Horn has illustrated this for the field. It comes out loud and clear in the PVDOMICS findings, which is that about a little more than a third of our patients fit into more than one WSPH group. The most common ones we're seeing are Groups 2 and 3; Groups 1 and 2; Groups 1 and 3; and Groups 1, 2, and 3. There is a lot of overlap.

Dr Berman Rosenzweig: I think it's been sort of amazing to watch that across the board. Back, I think, when the field was just in its early phases, the focus was on these pure Group 1 patients specifically, idiopathic PAH. We're seeing so many of these mixed phenotypes. That'll raise, I guess, the next set of questions about what to do with them and what's driving their disease and certainly I hope we will get some of these answers out of the omics work.

Dr Hill: As you know, we've done some preliminary work. So far with very small numbers, we're seeing a pretty high percentage of genetic abnormalities that we would expect to pick up in Group 1 patients in our Group 3s—25%, 30% of patients had some identifiable genetic abnormality.

Dr Berman Rosenzweig: Again, who knows what will evolve before the next symposium? I'm hoping there'll be some more updates to the classification system based on some of the findings from the omics work and hopefully a better understanding of these mixed phenotypes.

I think we're going to wrap it up. This has been awesome. I really appreciate your wisdom and experience in the field and being able to participate in this interview. Thank you so much.

Dr Hill: Thank you so much, Erika. I've really enjoyed speaking to you about it. Thanks for inviting me.

Dr Berman Rosenzweig: My pleasure. Again, thanks on behalf of PHA.

Risk Stratification—What's My Risk? A Practitioner's Tool

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At the 6th World Symposium on Pulmonary Hypertension, the task force on clinical risk stratification and medical therapy in pulmonary arterial hypertension (PAH) reviewed the latest developments published in the field of therapeutics since the previous meeting and presented their consensus opinions to an audience of 1376 participant attendees between February 27 and March 1, 2018, in Nice, France. After participants' input was incorporated, the final recommendations were published in the *European Respiratory Journal*.[1]

In the past several years, treatment for PAH was based on several parameters to determine the severity of the disease and risk of progression and poor outcome. These parameters included New York Heart Association Functional Class (NYHA FC), exercise capacity represented by the 6-minute walk distance (6MWD), and echocardiographic and hemodynamic measurements. Until recently, the guidelines for initiation and escalation of therapy relied mostly upon NYHA FC.[2] However, data from 3 independent registries demonstrate the importance of a methodical risk assessment and treatment strategy in PAH patients. All registries prove that, in order to obtain a good outcome (assessed as event-free survival at 1 year), patients need to achieve a low-risk status.

DEVELOPMENT OF RISK ASSESSMENT TOOLS FROM VARIOUS REGISTRIES

The task force evaluated several risk scores developed from the US and European registries: the French Pulmonary Hypertension Network (FPHN) registry risk equation,[3,4] the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk equation[5] and risk score,[6,7] the Swedish PAH Register,[8] and the COMPERA Registry.[9] They also evaluated the PH connection equation,[10,11] the Scottish composite score,[12] and the previous 2015 European Society of Cardiology and the European Respiratory Society PH guidelines.[2] We will briefly review the main 3 risk scores (FPHN, Swedish/COMPERA, and REVEAL), and point out some of their differences, advantages, and disadvantages for the practitioner. All risk calculators demonstrated good discrimination for long-term outcome.

The Swedish/COMPERA Risk Calculator

The Swedish PAH Register[8] and COMPERA[9] studies included both idiopathic and associated PAH patients and applied a risk score at baseline and at the first follow-up. A table of the variables is presented in Table 1. The risk calculator assigns a score of 1, 2, or 3 to each criterion (1 = low risk, 2 = intermediate risk, and 3 = high risk) and calculates the mean of the available variables.

The French Risk Calculator

In the FPHN registry,[13] risk assessment was performed in incident idiopathic, heritable, and drug-induced PAH patients according to the presence of 4 low-risk criteria: (1) NYHA FC I or II, (2) 6MWD > 440 m, (3) right atrial pressure < 8 mm Hg, and (4) cardiac index ≥ 2.5 L/min/m^2. Patients were classified according to the number of low-risk criteria present at baseline or at the time of reevaluation. As exploratory analyses, the additive value of brain

Table 1. Variables used in the Swedish/COMPERA calculator[a]

Variables	Low risk, score = 1	Intermediate risk, score = 2	High risk, score = 3
NYHA FC	I/II	III	IV
6MWD, m	>440	165–440	<165
BNP, ng/L	<50	50–300	>300
NT-proBNP, ng/L	<300	300–1400	>1400
RAP, mm Hg	<8	8–14	>14
CI, L/min/m^2	≥2.5	2.0–2.4	<2.0
SvO_2, %	>65	60–65	<60

Abbreviations: 6MWD = 6-minute walk distance; BNP = brain natriuretic peptide; CI = cardiac index; NT-proBNP = N-terminal precursor of brain natriuretic peptide; NYHA FC = New York Heart Association Functional Class; RAP = right atrial pressure; SvO_2 = mixed venous saturation.

[a]Adapted from Hoeper et al.[9]

Key Words—pulmonary arterial hypertension, risk stratification, treatment algorithm
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Disclosure: The author has no relevant personal financial relationships to disclose.

natriuretic peptide (BNP) < 50 ng/L or N-terminal pro-BNP (NT-proBNP) < 300 ng/L plasma levels or mixed venous saturation (SvO_2) > 65% as low-risk criteria was assessed in the subsets of patients for whom these data were available.

The REVEAL Risk Calculator

The initial score was developed from a US-based cohort of 2716 PAH patients, used 12 modifiable and nonmodifiable parameters measured at baseline, and provided the 12-month likelihood of survival (5 strata) in incident and prevalent idiopathic and associated PAH patients.[5] The REVEAL score has been validated in incident patients.[14] If used at follow-up, the equation can predict outcome at 1 additional year.[7] The REVEAL 2.0 score is an updated variation using fewer parameters and is more user friendly.[15] Although at the time of the symposium the updated version had not been published, here, we present the updated version in Table 2.

COMPARISON OF VARIOUS RISK ASSESSMENT TOOLS

The 3 risk calculators provide good discrimination for low, intermediate, and high risk (Table 3), REVEAL 2.0 having the highest discrimination score. The FPHN risk assessment strategy provides an accurate and easy identification of patients with an excellent long-term survival. The French score is the easiest to apply, having only 4 variables obtained noninvasively, although it has been developed only in idiopathic, heritable, and drug-induced PAH. The goal of the French score is to identify patients who do not need escalation of care. The downside is that a minority of patients achieve this very low-risk status, and the French calculator does not give any insights as to how to modify the treatment of those patients who do not fall into the very low-risk category. On the other hand, the other scores have been tested in both idiopathic and associated PAH. REVEAL 2.0 has the most variables and is the only one to include all-cause hospitalizations within the previous 6 months and the presence of renal failure, both of which have been shown to impact mortality.[16,17]

Table 2. Variables included in the updated REVEAL 2.0 risk calculator[a]

Variables			
WHO Group I subgroup	CTD-PAH	POPH	Heritable
	+1	+3	+2
Demographics	Male age > 60 years		
	+2		
Comorbidities	eGFR < 60 mL/min/1.73 m^2 or renal inefficiency (if eGFR is unavailable)		
	+1		
NYHA FC	I	III	IV
	–1	+1	+2
Vital signs	SBP < 110 mm Hg		HR > 96 BPM
	+1		+1
Hospitalizations	All-cause hospitalizations within 6 months		
	+1		
6MWD	≥440 m	320 to < 440 m	< 165 m
	–2	–1	+1
BNP or NT-proBNP	BNP < 50 pg/mL or NT-proBNP < 300 pg/mL	200 to <800 pg/mL	BNP ≥ 800 pg/mL or NT-proBNP ≥ 1100 pg/mL
	–2	+1	+2
Echocardiogram	Pericardial effusion		
	+1		
Pulmonary function test	D_LCO < 40% predicted		
	+1		
Hemodynamics	mRAP > 20 mm Hg within 1 year		PVR < 5 Wood units
	+1		–1

Abbreviations: D_LCO = diffusion capacity for carbon monoxide; CTD-PAH = connective tissue disease associated pulmonary arterial hypertension; eGFR = estimated glomerular filtration rate; HR = heart rate; POPH = portopulmonary hypertension; PVR = pulmonary vascular resistance; SBP = systolic blood pressure; WHO = World Health Organization. For other abbreviations, see Table 1.

[a]Adapted from Benza RL, Gomberg-Maitland M, Elliott CG, et al.[15]

Table 3. Comparisons between the risk calculators[a]

	REVEAL 2.0	Swedish PAH Register	COMPERA	French PH Network
Variables	12	8	8	4
Patients at baseline, n	2529	530	1588	1017
Patients at follow up, n		383	1094	1017
Type of PAH	IPAH, APAH	IPAH, APAH	IPAH, APAH	IPAH
Definition of low risk/ intermediate/high	6/7–8/9–12	Low: <1.5	Low: <1.5	Low: 3 or 4
1 year mortality by risk group (low/intermediate/ high), %	2.0/5.0/60.0–10.0	1.0/7.0/26.0	2.8/9.9/21.2	1.0/NA/13.0–30.0

Abbreviations: APAH = associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NA = not applicable.

[a]Adapted from Galié et al.[1]

In conclusion, there is strong relationship between risk stratification and outcome. The recently developed risk assessment tools help guide the treatment strategy for PAH based on disease severity as assessed by a multiparametric risk stratification approach. These risk scores are intended to complement the clinician's clinical judgment for any individual patient. Clinicians can now apply various risk scores in everyday practice depending on the type of PAH patient and choose the appropriate combination therapy or monotherapy (for a minority of patients). Further treatment escalation is required if low-risk status (considered as treatment goal) is not achieved in structured follow-up assessments.

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Pulmonary Hypertension Due to Left Heart Disease—Combine or Not Combined? DPG In or Out? A Practical Approach to the Patient With Suspected Left Heart Disease

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Pulmonary hypertension (PH) due to left heart disease (LHD) is the most common cause of PH in clinical practice. The definition and classification of PH-LHD has evolved in the last 5 years from the 5th World Symposium on PH (WSPH) in 2013 to the most recent 6th WSPH in 2018. Differentiation of PH-LHD, especially PH due to heart failure with preserved ejection from pulmonary arterial hypertension and chronic thromboembolic PH, can be very challenging. Finally, there is unclarity on the role of pulmonary vasodilators in the treatment of PH-LHD. The 6th WSPH consensus proceedings addresses all these topics in a detailed manner. In this article, we review the changes proposed by the 6th WSPH consensus proceedings in the definition, classification, diagnostic evaluation, and treatment of PH-LHD.

INTRODUCTION

Pulmonary hypertension due to left heart disease (PH-LHD), also known as Group 2 pulmonary hypertension (PH), is the most common form of PH in clinical practice.[1] The increase in pulmonary capillary wedge pressure (PCWP) due to LHD initially causes a passive elevation in the mean pulmonary artery pressure (mPAP) that is reversible with a reduction in left-sided filling pressures. The passive increase in mPAP is not associated with precapillary vasoconstriction or remodeling and is referred to as isolated postcapillary PH (IpcPH). However, some patients with IpcPH, over time, develop global pulmonary vascular remodeling including intimal thickening of the precapillary distal pulmonary arteries, arterioles, and the postcapillary venules, commonly referred as combined precapillary and postcapillary PH (CpcPH).[2] Both IpcPH and CpcPH lead to an increase in right ventricular pulsatile and static afterload, ultimately leading to right heart failure and death.[3] Thus, PH-LHD, regardless of the underlying LHD, is associated with increased mortality.[4,5] Compared to IpcPH, CpcPH is associated with worse exercise capacity, reduced survival, different genetic makeup, and closer phenotypic resemblance to PAH.[5,6]

During the most recent 6th World Symposium on PH (WSPH) in 2018, experts in the field of PH-LHD reviewed the literature in the last 5 years and created consensus proceedings that summarized key findings, challenges, and new proposals on how to approach patients with PH-LHD.[7,8] In this article, we review the changes proposed by the 6th WSPH consensus document in the definition, classification, diagnostic evaluation, and treatment of PH-LHD.

DEFINITION OF PH-LHD

The 6th WSPH consensus proceedings have proposed important changes to the definition of PH-LHD. The proceedings define PH-LHD as mPAP > 20 mm Hg with a PCWP > 15 mm Hg.[8,9] Previously, an mPAP ≥ 25 mm Hg was used to define PH.[10] However, multiple recent observational studies show a linear increase in mortality with every 1 mm Hg increase in mPAP from a threshold value of 20 mm Hg.[11,12] Based on this, in the new proposed definition, the threshold value of mPAP to define PH is lowered to >20 mm Hg.[8]

The cutoff value for PCWP to differentiate postcapillary PH from precapillary PH remains at >15 mm Hg, similar to the previous definition. Since accurate measurement of PCWP is key for correct diagnosis of PH-LHD, the consensus proceedings provides multiple tips for proper PCWP measurement.[8] First, PCWP should be measured at mid a-wave in patients with sinus rhythm. In patients with atrial fibrillation, it should be measured at 130–160 milliseconds after the onset of QRS and before the v-wave. The mid a-wave in sinus rhythm and 130–160 milliseconds after the onset of QRS in atrial fibrillation represents end diastole, where PCWP should ideally be measured. Second, the proceedings continue to support the measurement of PCWP at end expiration.[8] Using computer-averaged mean PCWP can underestimate PCWP and lead to misclassification of postcapillary PH as precapillary PH.[13] The end-expiratory PCWP correlates more closely to left ventricular end diastolic pressure than computer-averaged mean PCWP.[14] Third, the document emphasizes the importance of zeroing the transducer properly at the midchest levels with the patient lying supine with legs flat. Fourth, the operator should take 3 PCWP values within 10% variation and average them. Fifth, if there is any question on the accuracy of PCWP, especially when it is higher than the expected value based on the patient's clinical profile, a PCWP saturation should be obtained. A PCWP saturation > 94%

Key Words—diastolic dysfunction, heart failure, right ventricle
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Disclosure: The author has no relevant personal financial relationships to disclose.

confirms true PCWP measurement. Alternatively, left ventricular end diastolic pressure should be measured through a left heart catheterization. Finally, the proceedings highlight the importance of a large v-wave. The presence of large v-wave is highly suggestive of underlying LHD, even in the presence of normal PCWP.[8]

CLASSIFICATION OF PH-LHD: CPCPH VERSUS IPCPH

The proceedings document also proposed important changes on how to classify PH-LHD as either IpcPH or CpcPH. The 5th WSPH proposed to use pulmonary vascular resistance (PVR) and diastolic pulmonary gradient (DPG) to classify IpcPH and CpcPH once a diagnosis of PH-LHD is confirmed by a PCWP > 15 mm Hg.[15] To make a diagnosis of CpcPH, one requires the presence of PVR ≥ 3 Wood units or DPG ≥ 7 mm Hg.

However, at the 6th WSPH, CpcPH is defined only based on PVR. CpcPH is defined as mPAP > 20 mm Hg with a PCWP > 15 mm Hg and a PVR ≥ 3 Wood units. DPG has been dropped from the definition.[8] This is based on the literature published in the last 5 years. Several large observational studies and a meta-analysis have documented that many hemodynamic variables predict mortality in patients with PH-LHD including mPAP, PVR, pulmonary arterial compliance, transpulmonary gradient (TPG), and total elastance either alone or in combination.[4,5,16–18] The results are mixed with some studies suggesting one variable being better than the others. Thus, the consensus document acknowledges that the hemodynamic definition of CpcPH is debatable, and there is no single good answer. To overcome the inherent limitations with pure hemodynamic definitions, as it is not always practical to phenotype patients based on a binary value of a single pressure measurement, the document appropriately recommends future studies to evaluate nonhemodynamic diagnostics such as echocardiogram, cardiac magnetic resonance imaging, epidemiology-based risk scores, or biomarkers including genomics, proteomics, and metabolomics to differentiate CpcPH from IpcPH.[8] The ongoing PVDOMICS study sponsored by the National Institutes of Health may hopefully provide some insight.[19]

DIAGNOSTIC EVALUATION OF PH-LHD

The 6th WSPH proceedings recommend a 3-step approach in the diagnostic evaluation of PH-LHD. The purpose of this 3-step approach is mainly to avoid misclassification of PH due to heart failure with preserved ejection fraction (PH-HFpEF) as pulmonary arterial hypertension (PAH). This has significant therapeutic and prognostic implications. None of the currently approved therapies for PAH are effective in PH-HFpEF, and in fact, some are detrimental with increased fluid retention.[20] In addition, this 3-step approach reduces unnecessary overtesting by identifying the right patient population that will benefit from invasive hemodynamic assessment with or without provocative measures.

Step 1: Identify the Clinical Phenotype of the Underlying LHD Associated with PH

The WSPH classification categorizes LHD associated with PH into 3 broad categories: heart failure with reduced left ventricular systolic dysfunction, heart failure with preserved left ventricular systolic function (HFpEF), and left-sided valvular heart disease (aortic and mitral valve disease).[9] PH in the presence of left ventricular systolic dysfunction or moderate to severe left-sided valvular heart disease makes the diagnosis of PH-LHD very straightforward. No further diagnostic evaluation is mandatory.

However, it can be very challenging to differentiate PH-HFpEF from other precapillary forms of PH, especially PAH or chronic thromboembolic disease (CTEPH). PAH and CTEPH patients can have cardiovascular morbidities such as diabetes, hypertension, hyperlipidemia, obesity, atrial fibrillation, and coronary artery disease, similar to PH-HFpEF patients.[21] In addition, PAH and CTEPH patients will have normal left ventricular systolic function, similar to PH-HFpEF patients.[21,22] Finally, PAH and CTEPH patients can have left ventricular diastolic dysfunction similar to PH-HFpEF due to interventricular dependence.[22,23] Thus, to diagnose PH-HFpEF accurately, the proceedings document recommends assessing the pretest probability of PH-LHD, which is the second step in the diagnostic evaluation.[8]

Step 2: Determining the Pretest Probability of PH-LHD

The consensus document categorizes patients into 3 different categories: low probability, intermediate probability, and high probability for PH-LHD based on the combination of 9 different noninvasive variables including age, presence of cardiovascular comorbities, presence of atrial fibrillation, prior cardiac intervention or structural LHD, electrocardiogram, echocardiographic findings, cardiac magnetic resonance imaging, and noninvasive cardiopulmonary exercise testing.[8] Table 1 lists the detailed criteria for each variable for each pretest probability category.

Patients in the low pretest probability category likely have precapillary PH either due to PAH or CTEPH and should undergo further workup for those conditions. Patients in the high pretest probability category probably have PH-LHD, and further evaluations, especially an invasive right heart catheterization, are not necessarily warranted to make the diagnosis, unless they are participating in a clinical trial. However, patients in the intermediate pretest probability category, especially those with abnormal right ventricular size or function, systemic sclerosis, or unexplained dyspnea, should undergo invasive hemodynamic testing with or without provocative measures to determine the exact etiology. This is the third and final step in the diagnostic evaluation of PH-LHD. Of note: this pretest probability categorization is based on prior observational studies and expert consensus but has not been prospectively validated.

Step 3: Invasive Hemodynamic Assessment With or Without Provocative Measures

The proceedings document recommends considering invasive hemodynamic testing in all patients in the intermediate probability group but strongly recommends it in intermediate probability

Table 1. Pretest probability of left heart disease[a]

Feature	High probability	Intermediate probability	Low probability
Age	>70 years	60–70 years	<60 years
Obesity, systemic hypertension, dyslipidemia, glucose intolerance, or diabetes	>2 factors	1–2 factors	None
Previous cardiac intervention∝	Yes	No	No
Atrial fibrillation	Current	Paroxysmal	No
Structural left heart disease	Present	No	No
Electrocardiogram	LBBB or LVH	Mild LVH	Normal or signs of RV strain
Echocardiography	LA dilation; grade >2 mitral flow	No LA dilation; grade <2 mitral flow	No LA dilation; $E/e' < 13$
Cardiopulmonary exercise testing	Mildly elevated V'_E/V'_{CO2}; EOV	Elevated V'_E/V'_{CO2}; EOV	High V'_E/V'_{CO2} slope; no EOV
Cardiac magnetic resonance imaging	LA strain or LA/RA > 1		No left heart abnormalities

Abbreviations: LBBB = left bundle branch; LVH = left ventricular hypertrophy; RV = right ventricle; LA = left atrium; EOV = exercise oscillatory ventilation; RA = right atrium; ∝ = coronary artery and/or valvular surgical and/or nonsurgical procedure.

[a]This table is reprinted with permission from Vachiery et al.[8]

patients with systemic sclerosis, right ventricular enlargement or dysfunction, or unexplained dyspnea.[8] These risk factors increase the likelihood of underlying PAH or CTEPH. The consensus document also suggest that the invasive hemodynamic assessments are better performed in PH expert centers because of the technical complexities and nuances involved. The presence of PCWP > 15 mm Hg (properly measured) on invasive hemodynamic assessment confirms the diagnosis of PH-LHD in an intermediate probability patient. In contrast, if the PCWP is between 13 to 15 mm Hg in an intermediate probability patient, PH-HFpEF is still a possibility, and these patients should undergo provocative testing either with exercise or volume challenge to attain the proper diagnosis.

With exercise hemodynamic testing, the proceedings document indicates using the cardiac output (flow) adjusted PCWP rather than using an absolute cutoff value of PCWP to diagnosis PH-LHD. What is an abnormal absolute PCWP during exercise is controversial, and the data are mixed. The consensus document recommends using PCWP/cardiac output > 2 mm Hg/L/min as an abnormal exercise PCWP, as this has been associated with increased serum N-terminal-Pro brain natriuretic peptide levels, reduced exercise capacity, and reduced heart failure free survival.[24]

Due to the complexity involved in exercise hemodynamic testing, the 6th WSPH consensus prefers volume challenge over exercise testing as a provocative measure.[8] PCWP > 18 mm Hg immediately after infusion of 500 mL of saline over 5 minutes is considered as abnormal response and is diagnostic of PH-LHD in patients with intermediate pretest probability.[8]

TREATMENT OF PH-LHD

The main treatment of PH-LHD is proper treatment of the underlying LHD.[10] The 6th WSPH proceedings document recommends strongly against the use of PAH-specific pulmonary vasodilator therapies in patients with PH-LHD. This is based on the lack of large, randomized, controlled trials showing safety and efficacy of pulmonary vasodilator therapies in patients with PH-LHD. In fact, 2 recent trials have reported negative results for pulmonary vasodilator therapies in specific subsets of PH-LHD patients. In the SIOVAC trial, sildenafil 40 mg 3 times a day for 6 months in patients with persistent PH after successful valve replacement or repair procedure at least 1 year before inclusion was associated with worse clinical outcomes.[25] Patients treated with sildenafil had worsening composite clinical score of death, hospital admission for heart failure, change in functional class, and patient global self-assessment.[25] In the Melody trial, macitentan 10 mg once a day for 3 months was associated with increased risk of fluid retention compared to placebo in 63 patients with CpcPH with no significant improvement in PVR, cardiac output, and N-terminal-Pro brain natriuretic peptide levels.[20] The majority of patients in the Melody trial had PH-HFpEF, and all patients had a left ventricular ejection fraction ≥ 30%.[20] Table 2 summarizes the recently completed as well as ongoing clinical trials for treatment of PH-LHD.

WHEN SHOULD WE DO ACUTE VASODILATOR TESTING IN PATIENTS WITH PH-LHD?

There is much uncertainty in clinical practice regarding the utility and clinical significance of acute vasodilator testing in patients with PH-LHD. The only clear indication for acute vasodilatory testing in patients with PH-LHD is in the context of cardiac transplantation in patients with end stage left ventricular systolic dysfunction. There is a linear increase in 30-day post-transplant mortality due to acute right ventricular dysfunction with increase in TPG > 15 mm Hg, PVR > 3 Wood units, and mPAP > 50 mm Hg.[26] Based on this, the current heart transplant guidelines recommend an acute vasodilator challenge if systolic pulmonary artery pressure is ≥50 mm Hg with either TPG ≥ 15 mm Hg or PVR > 3 Wood units and systemic systolic arterial pressure > 85 mm Hg.[27] Intravenous nitroprusside or milirinone are the 2 commonly used agents for acute vasodilatory challenge in patients with PH-LHD being evaluated for heart

Table 2. Clinical trials for PH-LHD[a]

First author or study	Study drug	Dose	Subjects, n	Duration	Population	Primary outcome	Result
Recently completed clinical trials							
Guazzi et al.[28] (NCT01156636)	Sildenafil	50 mg 3 times a day	44	12 months	HFpEF	PVR, RV performance, CPET	Improvement
LEPHT[29] (NCT01065454)	Riociguat	0.5, 1, or 2 mg 3 times a day	201	16 weeks	HFrEF	mPAP versus placebo	No change
Hoendermis[30] (NCT01726049)	Sildenafil	60 mg 3 times a day	52	12 weeks	HFpEF	mPAP versus placebo	No change
SIOVAC[31] (NCT00862043)	Sildenafil	40 mg 3 times a day	231	24 weeks	VHD	Composite clinical score	Worsening in active group
MELODY-1[20] (NCT02070991)	Macitentan	10 mg once daily	48	12 weeks	HF (LVEF > 30%); 75% HFpEF	Safety and tolerability	+10% fluid retention in active group
SOUTHPAW Oral treprostinil (NCT03037580)	Oral treprostinil	Sustained-release oral tablets for 3 times daily administration	310	24 weeks	LVEF ≥50%; RHC within 90 days of randomization; 6MWD > 200 m	Change in 6MWD from baseline to week 24	Stopped early due to low enrollment
Currently ongoing or planned clinical trials							
SERENADE (NCT03153111)	Macitentan	10 mg once daily	300	52 weeks	LVEF ≥ 40% and ESC-defined HFpEF; HF hospitalization within 12 months and/or PCWP or LVEDP > 15 mm Hg within 6 months; elevated NT-proBNP; PVD or RVD	% change from baseline in NT-proBNP at week 24	
SOPRANO (NCT02554903)	Macitentan	10 mg once daily	78	12 weeks	LVAD within 45 days; PH by RHC with PCWP ≤ 18 mm Hg and PVR > 3 WU	PVR ratio of week 12 to baseline	
DYNAMIC (NCT02744339)	Oral riociguat	1.5 mg 3 times a day	114	26 weeks	HFpEF; mPAP > 25 mm Hg and PCWP > 15 mm Hg	Change in CO	
HELP (NCT03541603)	Intravenous Levosimendan	0.075–0.1µg/kg/min for 24 h (weekly)	36	6 weeks	HFpEF; LVEF ≥ 40%; mPAP > 35 mm HG; PCWP ≥ 20 mm Hg, and 6MWD > 50 m	Change from baseline PCWP with bicycle exercise from baseline to week 24	
PASSION (not registered)	Oral tadalafil	40 mg once daily	320	NA	HFpEF; PH with PCWP > 15 mm Hg and mPAP > 25 mm Hg and PVR > 3 WU	Time to first event defined as HF-associated hospitalization (independently adjudicated) or death from any cause	

Abbreviations: HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; PVR = pulmonary vascular resistance; RV = right ventricle; CPET = cardiopulmonary exercising testing; mPAP = mean pulmonary artery pressure; VHD = valvular heart disease; HF = heart failure; LVEF = left ventricular ejection fraction; RHC = right heart catheterization; 6MWD = six-minute walk distance; LVAD = left ventricular assist device; ESC = European Society of Cardiology; NT-proBNP = N-terminal pro brain natriuretic peptide; PVD = pulmonary vascular disease; RVD = right ventricular dysfunction; LVEDP = left ventricular end diastolic pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; RVD = right ventricular dysfunction.

[a]This table is modified with permission from Vachiery et al.[8]

transplant.[27] Intravenous nitroprusside is used if the systemic vascular resistance is elevated, whereas intravenous milirinone is preferred in the presence of normal or low systemic vascular resistance. There is no clear indication for acute vasodilatory challenge with inhaled nitric oxide alone in patients with PH-LHD.

CONCLUSIONS

The proposed definition of PH-LHD has been changed. Mean PAP > 20 mm Hg with a PCWP > 15 mm Hg defines PH-LHD. PVR > 3 Wood units in

the presence of mPAP > 20 mm Hg and PCWP > 15 mm Hg differentiates CpcPH from IpcPH. DPG is no longer needed for the classification of CpcPH. A 3-step approach has been recommended for the diagnostic evaluation of PH-LHD. Careful hemodynamic assessment at expert centers should be considered in patients with intermediate pretest probability for PH-LHD. Treatment of underlying LHD continues to remain the main line of treatment for PH-LHD. Pulmonary vasodilator therapies are strongly not recommended in patients with PH-LHD at this time.

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Pediatric Pulmonary Hypertension on the World Stage: Do We Need Separate Neonatal Guidelines?

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In comparison with adult disease, pediatric pulmonary hypertension (PH) and related pulmonary vascular disease (PVD) remain relatively understudied and poorly understood.[1] Despite many advances over the past decades, PH continues to cause significant morbidity and mortality in diverse neonatal, pulmonary, cardiac, hematologic, and other systemic disorders of childhood.[2–6] Despite some similarities, many aspects of PH in children are distinct from adult PH.[1] Although new drug therapies are available for off-label use in pediatric PH, the long-term outcomes of children with severe PH often remain poor. Most clinical studies have emphasized the results of clinical trials in adult patients, yet PH in pediatrics can be devastating and often contributes to poor outcomes in diverse clinical settings in newborns, infants, and children.

Of several major challenges addressed in the recent 6th World Symposium on Pulmonary Hypertension (WSPH), one goal was to explore major issues regarding the pathobiology, diagnostic assessment, management, and outcomes of diverse childhood diseases associated with pediatric PH.[2] There are marked differences in the epidemiology of pediatric and adult PH, as well as very striking differences in function, structure, genetics,[7] and responsiveness to therapies between adults and children with PH.[8] Unfortunately, studies that address the safety and efficacy of PH therapies in children are rare, as most pharmaceutical studies have focused on the adult population and only in patients with a fairly limited range of associated conditions. Except for the use of inhaled nitric oxide therapy for neonates with persistent PH of the newborn (PPHN) as based on multicenter randomized trials,[9-11] nearly all of the current therapies for children remain almost exclusively based on results from adult clinical trials and small case series of the use of PH-targeted therapies.[8] Thus, pediatric PH has been understudied, and little is understood regarding the natural history, mechanisms of disease, and treatment of childhood PH, especially in the setting of neonatal and genetic developmental lung diseases.

DEVELOPMENTAL LUNG DISEASES

At the WSPH, the Pediatric Task Force summarized many unique features that distinguish pediatric and adult forms of PH, especially as related to classification, diagnosis, and treatment.[2] Most importantly, pediatric PH is intrinsically linked to issues of lung growth and development, including many prenatal and early postnatal influences.[7,8,12–16] Pediatric PH often presents in the immediate neonatal period, which led to its own specific disease classification in Group 1 disease as PPHN.[2] The Pediatric Task Force further emphasized that PPHN represents a syndrome that is composed of specific diseases, ranging from its most common form as a transient disease after birth of term or near-term infants to more severe forms that include diverse developmental lung diseases and specific genetic disorders (Tables 1 and 2). Some of the major recommendations of the Pediatric Task Force were to further expand the classification and characterization of developmental lung diseases within the Group 3 disease category. These diseases include genetic abnormalities of lung development, such as alveolar capillary dysplasia (due to genetic mutations of the *FOXF1* gene), surfactant protein gene mutations (such as surfactant protein C, *ABCA3*, and others), and more recently, abnormalities of the *TBX4* gene.[12]

These developmental lung diseases often present during the early postnatal period and are frequently associated with severe PH with marked growth abnormalities of the distal lung (Figure 1). These disorders commonly present clinically in infants who are born at term or near-term gestation, with the clinical presentation of hypoxemic respiratory failure and severe PPHN physiology that is characterized by profound hypoxemia and elevated pulmonary vascular resistance leading to extrapulmonary shunting of blood across the ductus arteriosus and/or foramen ovale. PH in these infants may be poorly or only partly responsive to inhaled nitric oxide and other PH-tar-

Key Words—pediatric pulmonary hypertension, bronchopulmonary dysplasia, Down syndrome, angiogenesis, developmental lung diseases
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Disclosure: The authors have no relevant personal financial relationships to disclose.

Table 1. Developmental lung disease associated with pulmonary hypertension

Developmental Lung Diseases Associated with Pulmonary Hypertension
• Bronchopulmonary Dysplasia
• Congenital Diaphragmatic Hernia
• Down Syndrome
• Alveolar Capillary Dysplasia with Misalignment of Veins (e.g., FOXF1 gene)
• Lung Hypoplasia, Acinar Dysplasia
• Surfactant Protein Abnormalities
- SPB deficiency
- SPC deficiency
- ABCA3
• TTF-1/Nkx2
• TBX4
• Pulmonary Interstitial Glycogenosis
• Pulmonary Alveolar Proteinosis
• Pulmonary Lymphangiectasia

Table 2. Pulmonary vascular disease (PVD) in preterm infants: clinical phenotypes

Pulmonary Vascular Disease in Preterm Infants: Clinical Phenotypes
• **Early PH: (*Delayed Adaptation of the Lung Circulation at Birth)*:**
- ***Severe hypoxemic respiratory failure with extrapulmonary R-L shunt***
- ***Different patterns of delayed transition***
- ***Early echo findings of PH as a biomarker for worse late outcomes***
• **Late PH: (weeks to months)**
- ***High levels of respiratory support, supplemental O_2***
- ***Escalating respiratory care, recurrent cyanotic episodes***
- ***Echocardiogram findings of PH* at 36 weeks corrected age in stable infant**
- **Presentation after NICU discharge (with respiratory infection, PVS or progressive lung disease)**
• **Sustained PVD across the lifespan:**
- **PVD and cardiovascular disease in former preterms in older children and young adults**

geted drugs, or may respond to therapy but are unable to wean support during the newborn intensive care unit hospitalization. Histologically, these infants have marked parenchymal lung disease, as manifested by alveolar growth arrest with decreased surface area, variable degrees of hypercellularity and interstitial disease, reduced pulmonary vascular density, and signs of hypertensive remodeling of small pulmonary arteries (Figure 1). Current diagnostic approaches include genetic studies, chest computed tomography, and lung biopsy, with serial echocardiograms, measurements of N-terminal precursor of brain natriuretic peptide, and cardiac catheterization often included in the evaluation. Clinical course and outcomes are generally poor but can be highly variable, as case series for these rare disorders are somewhat limited. Some infants are candidates for early lung transplantation but experience is often limited to few centers with sufficient experience in treating young infants.

At the 6th WSPH, the Pediatric Task Force decided to include Down syndrome within the Group 3 classification as a developmental lung disease, except in Down syndrome subjects with anatomic congenital heart disease.[2] This decision was partly based on observations of the high rate of PPHN in Down syndrome subjects, and that abnormalities of lung development, including reduced alveolarization, decreased vessel density, persistence of the double-capillary network, prominent bronchial-pulmonary collateral shunt vessels, and hypertensive arterial remodeling, were often found in infants with PH.[13,14] In human fetal and neonatal lung specimens, Galambos et al. measured lung gene expression of anti-angiogenic factors, including *COL18A1* (endostatin), *COL4A3*, *TIMP3*, and *APP*, that are known to be expressed on Chromosome 21 (Figure 2).[15] They reported that these genes are overexpressed in Down syndrome lungs and that fetal lung vessel growth is decreased in subjects with Down syndrome. It appears that increased fetal lung anti-angiogenic factor expression due to trisomy 21 impairs lung vascular growth and signaling, which impairs alveolarization and contributes to high risk for pulmonary arterial hypertension during infancy.

PERSISTENT PH OF THE NEWBORN (PPHN)

The Pediatric Task Force further emphasized the need to recognize that PPHN, which has more traditionally been linked almost exclusively with term neonates in the past, can also occur in preterm infants (Table 2). In fact, recent studies suggest that the rate of PPHN is inversely related to gestational age at birth.[16] While PPHN typically resolves within the first months of life, the impact on later lung vascular growth and function remains unclear and warrants further study. Recent editorials and early reports have suggested that early disruption of vascular growth may increase the susceptibility of the adult pulmonary circulation for late onset of PH (e.g., "PVD across the lifespan").[17]

PVD IN BRONCHOPULMONARY DYSPLASIA (BPD)

Recent improvements in perinatal care have improved the survival of extremely premature infants, but nearly 45% of preterm infants develop bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, which is often associated with PH.[18] Prospective cohort data suggest that roughly 25% of preterm infants less than 32 weeks of

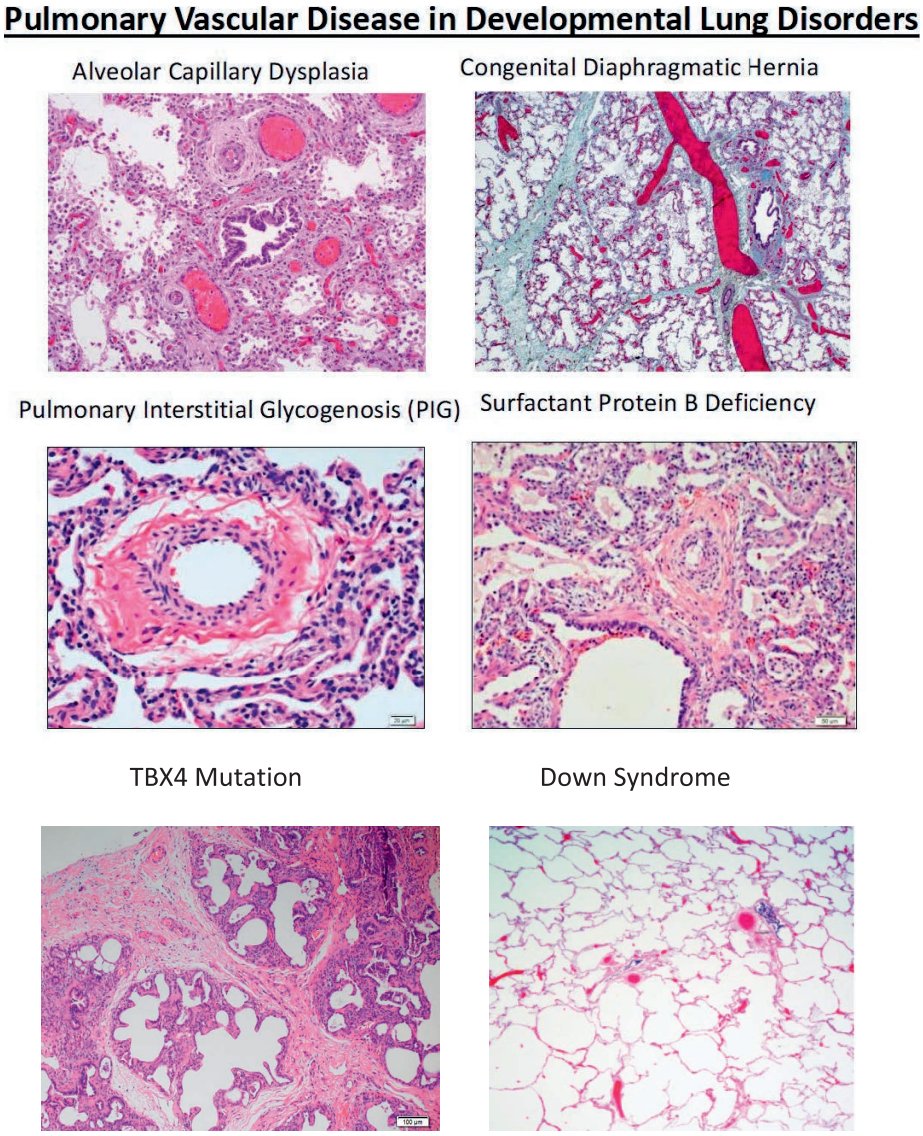

Figure 1: Histologic examples of diverse developmental lung disorders associated with severe pulmonary hypertension during early infancy.

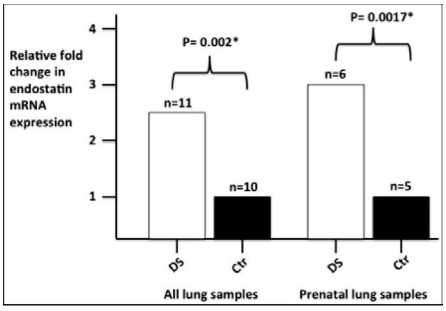

Figure 2: Increased lung endostatin gene expression in the human fetus and infant with Down syndrome. Comparisons between lungs from Down syndrome (DS) and non–Down syndrome (Ctr) subjects) are shown.

gestation at birth have echocardiographic evidence of PH at 36 weeks postmenstrual age and that PH is present in nearly 50% of preterm infants with severe BPD[18] (Figure 3). Despite the growing off-label use of PH-targeted therapies in preterm infants with PH, data are limited to best define clinical care strategies, and mortality remains high. Importantly, PH occurs most commonly in severe BPD, and the natural history and response to therapy is variable, reflecting the complex interaction of prenatal and postnatal factors that contribute to the pathobiology of BPD-associated PH.

In addition to postnatal lung injury, antenatal stress related to placental insufficiency with intrauterine growth restriction contributes to high risk of later PVD, highlighting the importance of early lung development.[19–23] Antenatal factors, such as chorioamnionitis, preeclampsia, and others, are strongly associated with an increased risk for BPD, especially when associated with intrauterine growth restriction as a biomarker for severe placental dysfunction and fetal stress. In addition to risk for PH, preclinical data suggest that disruption of angiogenesis impairs alveolarization in the developing lung.[24–26] Early changes in circulating angiogenic peptides, including decreased pro-angiogenic factors, increased anti-angiogenic factors (including sFlt-1, an endogenous vascular endothelial growth factor inhibitor that is markedly increased in blood and amniotic fluid of women with preeclampsia), and decreased endothelial progenitor cells, are associated with both abnormal placental vascular disease and high risk for BPD and PH. These data support the hypotheses that antenatal mechanisms that promote an anti-angiogenic fetal environment contribute to high risk for BPD and PH in preterm infants and suggest novel targets for disease prevention. Prospective clinical studies support these hypotheses, as early echocardiogram changes suggesting PVD at Day 7 of postnatal life is strongly associated with high risk for subsequently developing BPD or PH at 36 weeks corrected age, as well as late respiratory disease during childhood.[27–29]

LONGITUDINAL OUTCOMES OF EARLY PVD IN OLDER SUBJECTS

Postnatal growth of the pulmonary vascular bed during infancy and childhood is also important and may be the critical factor allowing for improvement of PH over time in a significant subset of children with BPD and PH. Long-term impact was highlighted recently in a study in which PH and pulmonary arterial stiffness were diagnosed by right-heart catheterization in a small cohort of young adults with a history of BPD during infancy.[30] These investigators identified that nearly half of their cohort had mean pulmonary artery (PA) pressures at rest that were above 20 mm Hg. This is especially important as the 6th WSPH recommended that the new

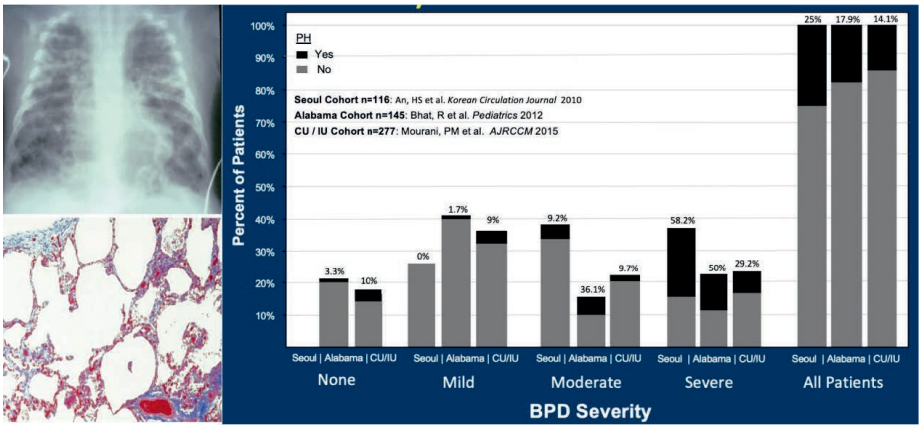

Figure 3: Bronchopulmonary dysplasia (BPD): radiologic and histologic features (left panel) and the incidence of BPD-associated pulmonary hypertension according to disease severity.

threshold value used to diagnose PH should be changed to measuring a mean PA pressure >20 mm Hg for children, with a continued emphasis on use of indexed pulmonary vascular resistance >3 WU*m^2. However, data are currently lacking regarding the impact of what was previously called "borderline" PH (mean PA pressure 21–24 mm Hg) in infants and children, especially in former preterm infants. Whether more aggressive monitoring and intervention of former preterm infants who meet this hemodynamic definition would improve cardiorespiratory function or obviate later PH is currently unknown. Further study will be necessary to determine any life-long consequences of early PVD as this population of infants and children enter adulthood.[17]

CONCLUSIONS

During the 6th WSPH, the Pediatric Task Force raised many questions regarding the growing importance of diverse developmental lung disorders associated with PH in the term and preterm newborn, including such diagnoses as PPHN, BPD, congenital diaphragmatic hernia, and several genetically based abnormalities of lung development. Critical gaps that limit our care for children with these diseases include the need for more extensive mechanistic preclinical work to better define developmental signaling pathways that regulate normal lung vascular growth and how disruption of these pathways leads to aberrant growth, function, and high risk for PH. In addition, there remains a need for better clinical characterization of the disease phenotypes that may set the stage for clinical trials that target infants with Group 3 disease. Current knowledge is limited for how to best intervene at early stages of disease that may lead to novel preventive strategies in preterm infants at risk for BPD, as well as better therapies beyond PH vasodilator drugs alone to improve outcomes of children with developmental lung disease.

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Behind the Scenes at the World Symposium on PH 2018

This fall, Guest Editor Erika Berman Rosenzweig, MD, Professor and Director of the Pulmonary Hypertension (PH) Comprehensive Care Center at Columbia University Medical Center, gathered a group of PH specialists by telephone to discuss some key events and topics from the World Symposium on PH 2018. The participants included Vallerie McLaughlin, MD, Professor and Director of the PH Program at the University of Michigan; Greg Elliott, MD, MACP, Chairman of the Department of Medicine at Intermountain Medical Center in Murray, Utah; Robert Frantz, MD, Professor of Medicine and Director of the PH Clinic at the Mayo Clinic; and Nicholas Hill, MD, Professor and Chief of Pulmonary, Critical Care and Sleep Division at Tufts University School of Medicine.

Dr Berman Rosenzweig: It's my pleasure to host this roundtable for *Advances in Pulmonary Hypertension* with some key experts in PH joining me. Our focus today is to provide a roundup from the latest 6th World Symposium on Pulmonary Hypertension (WSPH) meeting that was held in Nice, France, in 2018. The intent is to provide some additional insight on the meeting to the PH community from key leaders in the field. I want to start with a brief introduction of our expert panel.

We are joined by Dr Val McLaughlin, who's a professor of medicine and director of the PH program at the University of Michigan in Ann Arbor; the esteemed Dr Greg Elliott, who is also a leading expert, and has been for many years in the field of PH, having served as chairman of the department of medicine at Intermountain Medical Center amongst many other leadership positions in the field; Dr Bob Frantz, who is representing the Mayo Clinic as Director of the PH Clinic at Mayo; and Dr Nick Hill, who's the Chief of Pulmonary, Critical Care and Sleep Division and professor at Tufts University School of Medicine. This is, in my opinion, an all-star lineup, with so many years of experience between you all. We are so fortunate to have you all here to hear your impressions of the last WSPH meeting in 2018.

Dr Berman Rosenzweig: Val, I wanted to start with you because you've had such a big role as a WSPH Steering Committee member for this meeting and previous meetings, and personally knowing how much work and effort you've put in to make it a success. Could you please give us a quick introduction of the main goals of the world meeting and what you think were the main highlights from the most recent world symposium?

Dr McLaughlin: Sure, well, thanks for having me, Erika. The world symposium was a tour de force, it was a collaborative effort from experts all over the world that span different disciplines from basic sciences to clinical care, from pathologists to cardiologists and pulmonologists; it was really a very special meeting. I think each time we have a symposium every 5 years, we want to not only highlight the new findings that have occurred in the prior 5 years, but dive deep into some areas and be provocative and I think that was the case at this particular meeting. I think the most provocative item that was discussed was the hemodynamic definition, and I imagine you're going to touch on that later, as well as some of the tweaks in the classification. I think one of my favorite things about this past meeting was the addition of the task force on the patient perspective. I think it's important not to lose sight of why we do this and to understand what the patients want. There were also important highlights in terms of the treatment algorithms and in terms of all the new genes that have been identified. I think one lesson that was most impactful in my practice is what came out of the genetics task force that Greg was on and how to apply all of the findings that we've had in genetics over the years to our patients. I've started to do a lot more referrals to genetic counselors and genetic testing since that symposium.

Dr Berman Rosenzweig: Yes, you've touched on so many important points and I'd like to hone in on some of them a little more. Provocative is a great word to describe the meeting, because I agree, and I'm sure other task force members would agree as well, that there were certain parts of the proceedings that have led to many further discussions since the WSPH meeting and I think that's part of the process and part of the goal, to generate discussions for the scientific community and for future meetings. I'd like to start specifically by asking the other panel members about their thoughts on the update to the hemodynamic definition with the proposed modification to define PH as when the mean pulmonary arterial pressure (mPAP) is greater than 20 mm Hg and the pulmonary vascular resistance (PVR) is greater than 3 Wood units. I'd like to get your thoughts about how that might impact clinical practice.

Dr Elliott: I'll start because then people can push back. I mean, I view the catheterization as a diagnostic test, maybe like a pulmonary function test, and I'm fine with accepting a definition built around what we know are normal pulmonary hemodynamics. I think the subtle issue for me is going to be knowing when to diagnose the disease, and I think the catheterization or the numbers that we pick, an mPAP greater than 20 mm Hg, obviously for me just doesn't translate to diagnosing disease in a patient. For me, that would be the key starting point on the new definition.

Dr Frantz: It's been really fascinating to me because I've had the opportunity

to be involved in a number of sessions about the new definition, debating about whether it should be incorporated. Right now I'm actually doing a Point/Counterpoint piece with Dr Brad Maron**,** which will be published in *Chest* relatively soon, about whether the new definition should be embraced in clinical practice, and I think you're spot on in terms of talking about hemodynamic catheterization as only one element of what goes into a diagnosis of pulmonary arterial hypertension (PAH). I think that part of the impetus was of course the goal of earlier diagnosis of PAH, although the majority of problems with early diagnosis do not have to do with the hemodynamic definition, they have to do with failure to think of the disease process and pursue testing to find it, as opposed to seeing a lot of patients who can meet this new definition that before were being ignored in some way. So I don't think that the goal of earlier diagnosis will be served in a broad context that well by the change in definition, although there will be some patients; and I think context is really everything. If a patient has scleroderma and you're doing a right-heart catheterization at 4:00 pm, and they have been fasting all day and they're on a diuretic with a wedge of 4 mm Hg, then they can easily have an mPAP of 22 or 24 and still have a PVR over 3 Wood units and very likely do have significant pulmonary vascular disease. On the other hand, there's opportunity for mischief here too, where there could be a fair number of patients who have borderline elevation of PVR and who have a lot of hypoxemic lung disease or have some tendency to heart failure with preserved ejection fraction with borderline wedge pressure, and that could easily be miscategorized because we don't really have a good nonbiopsy biomarker of the pulmonary vasculature to say that there is true Group 1 pathology. I do like the concept of calling attention to findings that are outside the bounds of normal, and I think that makes sense with an mPAP between 20 and 25 mm Hg, that that's really not normal. On the other hand, there are an awful lot of different situations that can result in that pressure and so if it's misapplied in clinical practice, it could cause a lot of mischief with overdiagnosis and psychological anxiety and all the rest of that for causing that kind of concern about PAH when maybe they don't really have PAH.

Dr Hill: I agree with what Greg stated about how the upper limit of normal doesn't necessarily define a disease. According to the Kovacs study, a meta-analysis on over 1000 catheterizations in healthy individuals that was published in *European Respiratory Journal* in 2009, the mPAP was 14 mm Hg and 2 standard deviations above that was 20 mm Hg; so I don't think we can argue that the definition of normal is fairly clearly established by that. The problem is, how do you define disease, and are there multiple diseases?

Another problem is that even though there are studies that have shown increased morbidity and mortality in that borderline group with mPAP of 21 to 24 mm Hg compared to patients with lower pulmonary arterial (PA) pressures—we don't understand the pathophysiology; there may be multiple things going on there, and it's really just an association at this point. We don't understand whether these people should be treated and whether they respond to any treatments, so we simply don't know enough, I think, about this group to change the definition at this point.

One other problem that is inherent in the definition that was proposed was picking the PVR of 3 Wood units. If the committee wanted to adhere to the same rationale for picking 20 mm Hg as the upper limit of normal for mPAP based on the Kovacs study, the average PVR in normals in that study was actually about 0.9 Wood units; 2 standard deviations above that and you get 1.66 Wood units, so 3 is quite a bit higher than that, and if you adhere to 3, you're going to have a hard time finding many people whose PVRs are 3 or greater who are alive, because the transpulmonary gradient becomes fairly narrow when you lower the definition like that, and the only way you get a PVR that high is to have people whose cardiac outputs are pretty low.

Dr Frantz: What I've seen that way, is you sometimes see underestimation of cardiac output. I've seen a couple of patients in the last year already who had a cardiac output that was estimated by indirect Fick, and that inadequate technique resulted in underestimation of cardiac output, overestimation of PVR, and the patients ended up on 2 different PAH therapies, felt no better, and clearly did not have the correct diagnosis, so it is certainly tricky in that way. I've also had patients who had a PVR that was borderline and I gave them nitric oxide and they completely normalized, and so we don't really think about giving nitric oxide to patients in that borderline category but if you do it, you'll find some that are actually just vasoconstricted and maybe that's a completely different problem as well.

Dr Hill: I was just going to say that because of the PVR problem, it's actually very hard to find patients who meet the criteria, and there was a pro/con in *European Respiratory Journal* in April earlier this year; I think Adam Torbicki was the first author of the con, and he pointed out that when they looked at patients from Hammersmith, in London, and also at his place in Poland, amounting to several thousand patients, only about 1% to 2% of the patients actually met this definition.

Dr Frantz: That's true. Dr Gerry Coghlan of Royal Free Hospital in London has done a nice subanalysis of the Detection of PAH in Systemic Sclerosis (DETECT) registry, and also demonstrated that patients who are borderline are only slightly more likely to end up meeting the classical criteria over the next 3 years than patients who were initially not so borderline, so I think, as a marker of patients that are going to go on to have PAH, it's also imperfect even in the scleroderma world.

Dr Berman Rosenzweig: Another great point. Val, do you want to chime in here, because I'm sure you have an opinion as well and we would like to hear your thoughts.

Dr McLaughlin: It's a great discussion. You guys are right. These patients are extraordinarily rare. In fact, just in the *European Respiratory Journal* in the past

month or two we published our series of patients that we have screened with scleroderma and we've done a lot of right-heart catheterizations. If you look at all of the right-heart catheterizations we've done for this over the past few years, you'll find one or two additional patients who would be diagnosed with that new definition. It's extraordinarily rare. But I think Nick made a good point about the PVR, and I wouldn't be surprised if that topic gets taken up at the next world symposium.

Dr Hill: I'm sure you're right.

Dr Berman Rosenzweig: These are great points. I wonder in terms of your clinical practices and research, between let's say now and when there may be further official discussions, if you come across one of these patients who falls into this hemodynamic range (mPAP 21 to 24 mm Hg, and PVR > 3 Wood units), would you just observe them, treat them, collect data, create research around this topic? What do you plan to do?

Dr Frantz: Well, I think, being fair to the guidelines, they do very clearly state that this new definition does not imply treatment of these patients in any specific way and so that's clear cut and well stated. On the other hand, the idea of exercise-induced PH kind of continues to fail to make the grade even though things that to me are just about as borderline as PVR of 3 are being incorporated. In my mind, if anything, I'm finding we're doing more exercising hemodynamics, and if you have somebody whose borderline PAP goes to 100 mm Hg with exercise, and the cardiac output response is impaired, then that patient very likely does have pulmonary vascular disease as opposed to others where the PVR actually falls and the PA pressure doesn't really go up, or the wedge shoots up and we really have heart failure with preserved ejection fraction. In my mind, I think we're being very careful to do super deep phenotyping with regard to vasoreactivity, exercise response, and understanding the phenotyping of these patients in a way that requires an expert center. It's just going to be much more difficult to do out in the routine clinical practice world.

Dr Hill: I think we need to study this group more carefully. I would get rid of the PVR greater than 3 Wood units requirement so that you can look at people whose mean PA pressures are greater than 20 mm Hg without that restriction. You'll get about 5 times, at least, as many patients, perhaps more, and they can be followed so that we can understand more about pathophysiology, about what's contributing to the increased mortality in this group.

Dr Berman Rosenzweig: This is really a great discussion and I'm certain it will continue on, and that by the next meeting we're also, as Val mentioned, continuing to debate and hopefully coming up with some additional modifications once we study this further. And to your point, Bob, about the exercise testing and what it means for exercise-induced PH certainly, that's still wide open for further study as well. I'm going to move on because I want to touch on another topic that I think is very important. I thought the addition of the phenotype of very robust, vasoreactive responsive patients into the diagnostic classification as a separate group in WSPH Group 1 was an important addition. All of you have many years of experience, and I'm sure have seen robust acute responders before, but it's surprising to me that those that who haven't seen as many WSPH Group 1 patients do not necessarily buy into this concept, and I just want to poll the group in terms of your impressions about the addition of that to the classification system, because I do think identifying these patients as having a different phenotype can be very important, not only for them but for awareness in the field. Does anybody want to respond to this addition?

Dr McLaughlin: Erika, I think it's a really valid point that this group is different; there's something different about them, whether they have more smooth muscle cell hypertrophy and vasoconstriction and less intimal proliferation, or they just have another abnormality, but they're a different group of patients. If they have that response, calcium channel blockers may be enough to have such a wonderful long term prognosis. I'm lucky if I see one or two of those a year in the referral practice that I have, but they're clearly different. I think my concern about the way the classification is done is, when do you put them in that classification or what if they lose responsiveness over time? Many of them, the true responders, don't lose responsiveness, but if they have that response at the time of their catheterization, you still need a trial period of calcium channel blockers to make sure they clinically respond, so there's some floating around of the actual nomenclature for an individual patient that we need to be cognizant of, but they're clearly a very different group.

Dr Hill: I agree. I think there are differences within the group, too. On one hand, you have the super responder patients that Val just alluded to, the ones we look for who are likely to be calcium channel blocker responders. I can recall one patient I saw years ago who started out with PA pressures of 100/40 mm Hg and in response to 5 ppm of nitric oxide, with every beat, the pressure came down and settled at 30/20 mm Hg over just a few minutes. I was concerned about removing the nitric oxide and the pressures went right back to 100/40 mm Hg going up with each beat. The patient didn't notice any difference at all, and she did very well on calcium channel blockers, not surprisingly.

On the other hand, another super responder I saw to epoprostenol was a woman who had similar pressures but was in florid right-heart failure, with a cardiac index of 1.5 L/min/m^2, and she went on 13 years, even though her prognostic factors would have said she should have lived less than 6 months at the time, and I know we've all seen these patients. She did not respond at all acutely, and yet her pressures virtually normalized, her mPAP dropped to 26 mm Hg, her PVR was well within normal limits and she died last year of a complication of another disease and not of PH, so that's another example of a super responder, not acutely vasoreactive, but obviously highly reactive to prostacyclins.

Dr Frantz: Nick, did you leave her on intravenous prostacyclins even though the PVRs had essentially normalized?

Dr Hill: Yes, I kept her on it.

Dr Frantz: I have a similar patient whom I met peripartum some years ago who was really in florid right-heart failure, not that acutely vasoreactive, and we treated with parenteral epoprostenol, and after several years when I did repeat catheterization, her PVR was flat-out normal and I thought, well, maybe she had a peripartum problem that's now gone. And so I actually weaned her off all of her PH therapy and she did all right for about a year and then that PA pressure started going back up again and I had to resume parenteral prostanoids**.** It was just crazy because we don't think of patients that are on parenteral prostenoids as having full normalization of PVR and so there was something about her that was very responsive to prostanoids in terms of being able to normalize PVR but did not maintain that with cessation of the therapy. I think at least identifying these kinds of unusual patients is valuable and maybe as we get better at metabolomics and genomics and proteomics, we'll be able to get signatures about those patients that tell us more about their disease state.

Dr Elliott: Erika, I've wanted to see this group identified and called out for a long time. The first one I had we tested with epoprostenol in the cath lab in 1984, and I'm happy to tell you she's still alive. And coming back to how we started our discussion, seeing a lot of this through the patient's eyes, when I met this young woman, she and her husband had been told she had a year to live. That was before the cath and acute vasoreactivity testing. They really are a unique group of patients; as I think Val mentioned earlier this year, we only see one or two of them a year if we're lucky but when you see it, it's different, and it's really important to call it out for the patient because it helps them to understand that they have a disease that's very often very treatable with a very good prognosis, unlike many of the other patients. So I was really glad to see it called out and of course, putting my genomics hat on for a minute, I've always talked about this as the vasoreactive phenotype with the idea that someday we'll figure out that genetic signature and really understand what this is all about, and maybe have, for better or worse, targeted therapy for it.

Dr Berman Rosenzweig: Yes, I couldn't agree more and that's why I think, even if it's a matter of working out some kinks as Val said, for example, with regard to if a patient subsequently becomes nonresponsive to acute vasodilator testing, what do you call them, the fact that they are identified as a separate group underscores what everybody on the panel has said, that if you've managed one of these patients, it's quite rewarding, because they can be so responsive to therapy. So personally, I was also glad to see them highlighted there and hope there will be more work done to identify, as you said, Greg, whether there is a particular genotype that's associated with robust responsiveness.

With that, I'd like to focus a little on the Genetic Task Force, which was a real highlight of the meetings. There has been a lot of exciting recent movement in the identification of other genes related to PH in both the adult and pediatric world, and I'd like everybody's thoughts in terms of how that might impact your clinical practices. Specifically, I'd say that we all probably have patients that we've seen for many years and we may have done genetic testing when we first met them, but I think there's an opportunity to resend genetic testing on many of these patients now. Is that what you're all doing and maybe you can share some of your thoughts on that?

Dr Elliott: I'll jump in and congratulate Val. Val took it home and Val's team is now doing the genetic testing and counseling, had a poster at PHPN that shows their work and I just thought it was fantastic.

Dr McLaughlin: Yes, thanks. I learned so much and I was able to practically apply it in our practice. Another point is the issue with pulmonary veno-occlusive disease (PVOD): when you're suspecting it, that *EIF2AK4* testing can be sent. We are doing that and we have found it very helpful, but I think another thing to emphasize is just the importance of the genetic counselor in this. I don't feel qualified to do that myself and those folks are really fantastic and make great contributions; they are an important part of our health care team now.

Dr Elliott: That's a wonderful point Val, absolutely wonderful.

Dr Berman Rosenzweig: Yes. Any other thoughts on this?

Dr Elliott: I would add about the *EIF2AK4*, just a point, and that is, when we've looked at this, and we've looked at it, our European colleagues have looked at it, the *EIF2AK4* mutation has also been found in very small numbers of patients diagnosed with classic Group 1 PAH, and so sometimes I think, even if you're not suspecting PVOD, you have to realize they may actually have heritable PVOD–pulmonary capillary hemangiomatosis and look like PAH.

Dr Berman Rosenzweig: That's really important. I think it was also highlighted, in terms of being a spectrum of disease now, that you can have features of PVOD, pulmonary capillary hemangiomatosis, and PAH. My one quick question is about the turnover and being able to get these genetic results quickly. So if you have a patient and you suspect PVOD, and they may be quite sick, and you're trying to determine whether you might list them for lung transplant, how quickly in the real world setting can you turn over these genetic results for the clinician?

Dr Elliott: I don't know that I've ever done one as a rush, I think that's one of the problems. I can't actually tell you the shortest time window that we could turn it around in our lab, but to have a result in a couple of weeks with the targeted gene panel would not be unusual.

Dr McLaughlin: I just want to say one of the things that we sometimes run into is just the insurance coverage, and then the cost if the insurance doesn't cover it.

Dr Berman Rosenzweig: Yes, that's an issue and of course, access for other smaller community hospitals and being able to do this from a practical standpoint, is definitely something that I hope folks will be working on in the near future, so that one could really translate this into clinical practice. Unfortunately, in the absence of a lung biopsy sometimes we're relying on explanted lungs to confirm the diagnosis if we highly suspect it, but the genetic testing could potentially turn into a clinical diagnostic tool. That's the hope for the future, so hopefully we can broaden and improve upon how this is put into clinical practice because it really can make the difference to the patient.

Dr Elliott: If I may add, even the 2015 European Respiratory Society/European Society of Cardiology guidelines pointed out that testing the *EIF2AK4* and finding pathogenic mutations is diagnostic. One doesn't need histopathology if you find that. When you don't have a critical patient and you suspect PVOD with PH, you don't need to do a lung biopsy. It obviously subjects them to mortality risk. Our own experience here—I figured it out one time and I actually looked at the cost at Intermountain of the lung biopsy that we had done compared to the genomic test, and we saved several thousand dollars by doing the genomic test over the lung biopsy.

Dr Berman Rosenzweig: That's a great point. One final focus here. Val mentioned the newly developed task force on patient perspective. I want to, first of all, commend you and your team for focusing on the patient perspective, because as you said, this is obviously the critical core of all that we do, and so I want to get the group's impressions on that as an addition to the last meeting, and hopes for the future with regard to patient input on future proceedings and meetings.

Dr Elliott: Once again I'll jump in and say hats off to Val and the organizing committee. Not only was it a terrific idea to include the patient perspective, which we all know often differs from the doctor's perspective or that of the medical professionals, but they also picked a terrific chair for that, Mike McGoon, and I thought Mike did an outstanding job.

Dr Berman Rosenzweig: Great, absolutely agree Greg.

Dr McLaughlin: Yes, I also agree. One thing I heard from them was that they really want to hear about palliative care at an earlier stage, and I personally have a challenge talking about that, especially earlier in the course of disease, because so many patients come to us for hope and we spend so much time doing everything we can. I tend to wait until I know I've exhausted my options and they're not a transplant candidate to bring up the concept of palliative care but it seems to me that they wanted to hear about it a little bit sooner.

Dr Berman Rosenzweig: That's a great point. I agree. I think that we are often faced with patients who've been told, at least in the early years, there are no options and we have always focused on providing options and hope for them. I think it's a little harder for some of us, at least for me, to introduce early on, but it was definitely a highlight of that task force.

Dr Hill: I think it really depends on how palliative care gets presented to patients. I've always thought that when we take care of patients with any chronic illness, we should be thinking along palliative care lines. We don't have cures for diseases like PAH and so the focus really needs to be on symptoms. Certainly we would like to extend survival as much as possible, but to help them get the most out of the life they have, that's really the focus of palliative care, and I think when presented from that perspective, that we're trying to enhance function and quality of life with palliative care, I think it's a nice, easier sell.

Dr Frantz: Nick, I think that's exactly right, that we try to take more of a parallel approach, where we say we're going to do everything that we have in our power, to the extent that you wish to do so, to treat your PH effectively; but there's another team that has much more expertise than we do about symptom management and the psychology of dealing with chronic disease and uncertainty, and we're going to take a parallel track where we're going to be holistic, and we're going to push forward with everything we know how to do medically, but here's another team, that's also part of *your* team, that will help you to deal with both side effects and issues that come up from a psychologic and adaptation perspective. With that, I think we've been able to make some inroads into helping patients see palliative care a little bit sooner and hopefully gaining from that. We started to incorporate quality-of-life instruments into our clinical practice now, in a way where we're doing the PAH Symptoms and Impact (SYMPACT) as a 1-day patient-reported outcome for patients coming to the clinic and trying to use that. Actually, my colleague Dr Hilary DuBrock has developed a research project of referring patients whose SYMPACT scores are high to palliative care or not in a randomized way, unless the clinician feels they absolutely need to see them, and to try to see whether that earlier referral based on SYMPACT scores might actually contribute to better quality of life and better patient adaptation to the disease. So I think this whole field of the patient-reported outcome and palliative care and patient-centered care is really critically important and moving faster than it has in many years.

Dr Berman Rosenzweig: Thank you. I think those are all terrific and insightful comments and I couldn't agree more that this is very important to the patients and families and we can all learn more—at least, certainly I can, as a practitioner, to implement this earlier on for patients. We're winding down, but I do want to take a moment to focus on your work, Val. You recently, with others, established an association for the next, and future, World Symposium on PH meetings called the WSPHA. I wanted to give you an opportunity to share the plans for that, and the goals of the WSPHA in terms of planning in between these WSPH meetings and to

share those with the community, if you don't mind.

Dr McLaughlin: Sure, thanks for giving me the opportunity to talk about that, Erika. Essentially, the leaders of the last world symposium looked at each other afterwards and said, "That was really interesting, there was a lot going on, I wish we would have had more time to think about this, or more time for interaction between this group and that group, or more continuity." So we decided to form this association that really, I hope, is going to help the every-5-year symposiums go on in perpetuity and have more continuity. We've already had a couple of meetings. We formed a large and what I believe is a very inclusive scientific committee that has broad representation, and we're starting to brainstorm some of the things that we think should be incorporated into the next meeting, forming some subcommittees to explore whether this idea is going to have enough data to discuss or whether we should be going in that direction. The increase in communication and planning is going to make the next meeting in 2023 even more rigorous, and maybe even more provocative. It's really been a pleasure to be a part of that and to be able to work with so many different folks who are being very thoughtful about the future of PH. I believe it will allow for more crosstalk between the committees. When you start planning this just a year or two in advance, the committees are all working hard and they're getting their work done, but sometimes you get there and they haven't shared some of their ideas with each other, and it makes it more of a challenge. This will be a really nice opportunity to have a little bit more thought going into some of the topics and a little bit more communication amongst the different task forces in between meetings.

Dr Berman Rosenzweig: Thank you, Val, I think that this is very exciting for everybody on the call and in the community, particularly regarding some of the questions that have been raised, and some of the thought-provoking areas of interest which can now be focused on in between meetings. I believe these discussions are so valuable in terms of planning ahead for the next WSPH and prompting research to answer some of these important questions.

It was an honor to lead this discussion and hear your insights. On behalf of the PHA and the *Advances* editorial board, I want to thank you all for your incredible wisdom and thoughts on the 6th WSPH meeting.

Bridging the Gap: A Multidisciplinary Approach to Transitions of Care

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INTRODUCTION

Pulmonary hypertension (PH) is a chronic, progressive heterogeneous disease that affects many individuals worldwide. Despite extensive research and therapeutic advances in the treatment of PH, the morbidity and mortality rates remain high, and this bears a significant economic burden on the health care system. PH-related morbidity is associated with disease progression and often requires hospitalization, which may be considered an important measure of clinical worsening.[1] Current US third-party reimbursement systems can penalize hospitals for hospital readmission. A coordinated multidisciplinary approach to hospital discharge is required for patients with PH.

HOSPITALIZATION AND PH

Approximately 200,000 hospitalizations occur annually in the United States with PH as a primary or secondary diagnosis.[2] Using the National Inpatient Sample Database to identify PH or cor pulmonale as the primary discharge diagnosis from 2000 to 2013, the authors found increased admissions for PH in terms of absolute numbers, mean length of stay, and hospital charges.[3,4] In fact, the overall cost of hospital visits of a patient increased by 209.5% from $301,324,218 in 2000 to $932,554,725 in 2013.[4] These inpatient costs associated with PH contribute significantly to the total health care burden. With advances in PH treatment options and increased use of combination therapy, medication costs are rising. However, these medication costs may be counterbalanced by reduction in hospitalizations.[5] Further research on cost-effective evaluation and management of PH is required.

Recent studies demonstrate that clinical worsening including all-cause hospitalization is associated with worse outcome.[6] Indeed, PH-related hospitalizations have been associated with a higher mortality rate in clinical care[7] and generally lead to higher health care costs related to diagnostic procedures and medications.[8] The REVEAL registry showed that a first hospital admission within 1 year of diagnosis portended a high likelihood of rehospitalization.[8] Another study noted 42% of hospitalized PH patients had at least 1 rehospitalization within the first year after discharge, some having numerous readmissions.[5] In addition, intensive care unit admission for PH has been associated with poor survival after discharge, with older age, baseline right heart failure, and severity of organ dysfunction as independent predictors of long-term mortality.[9] Close follow up is recommended for PH patients who survive critical illness. Moreover, particular caution should be used with PH patients hospitalized who are managed with parenteral prostacyclin therapy with regard to patient safety. Current studies demonstrate risk of serious and even fatal errors with intravenous prostacyclin therapy and recommend the development of standardized policies and treatment guidelines for each institution to reduce patient risk.[10]

Pulmonary arterial hypertension (PAH) treatment, including upfront combination therapy, may decrease morbidity and clinical worsening.[5] For example, in a post hoc analysis of the AMBITION trial, upfront combination therapy resulted in a 63% risk reduction for hospitalization related to PAH.[11] For every 9 patients treated with combination therapy, 1 hospitalization due to PAH may be prevented over 1 year's time.[11] Efforts to reduce hospital readmission rates may positively impact morbidity, mortality, and health care system financial burden. Increasing attention should be directed toward reducing PH readmissions and, importantly, identifying patients with the highest risk for readmission. By implementing individualized, multidisciplinary discharge planning early in hospital admission with a detailed plan for transitional care and close follow up, PH readmission rates may be positively impacted. The use of tools and checklists may enhance the PH team's ability to provide consistent, comprehensive posthospitalization care.

DISCHARGE PLANNING

Transition from hospital to home is deemed a high-risk period where patients may be at risk for developing adverse events during postdischarge phase.[12] Generally, the information that must be relayed at hospital discharge is often complex and overwhelming. Lack of clear communication has been implicated as a common finding, and pertinent information may not be sent to outpatient pro-

viders, which may have a negative impact on follow-up plan. Strategies to support patients returning home and to facilitate communication of information to local health care providers, including educating patients to carry a record of discharge summaries to local provider visits, may improve patient self-management and reduce rehospitalization.

Studies in heart failure and other medical illnesses have demonstrated that a single intervention is not sufficient to address the multifaceted discharge needs of complex patients.[13] Transition of care from inpatient to outpatient care should be individualized and multidisciplinary. Discharge planning should begin at the time of admission, including assessing patient and family knowledge, adherence to medical plan, and ability to manage care regimen. Often, important discharge information, such as medication changes and self-care strategies, is discussed at the time of discharge. This is a suboptimal time for patient education. Allied health personnel including advanced practice providers, pharmacists, nurses, and discharge planners are optimally suited to develop a plan of care for each patient, including self-care education plans for the patient and family to reduce risk of readmission.

Self-management and patient education are key components of discharge planning after hospital admission. Disease self-management is described as tasks an individual undertakes to live well with a disease condition, including medical management, learning meaningful behaviors and roles, and managing emotions of having a disease such as fear, anger, depression, and frustration.[13,14] This requires gaining an understanding of the disease, developing skills to manage treatment regimens and problem solve, making and maintaining lifestyle changes, and coping with a myriad of emotions. This may require changes in usual activities and finding additional support such as classes, counselors, medical team consultation, and support groups. Nurses in the hospital have numerous opportunities to make an impact on self-management skills for patients and families, as they have significant expertise in disease management, medication adherence, dietary modifications, social support, and symptom control. The inpatient PH nurse practitioner or physician assistant also plays a key role in developing and implementing the transition of care plan.

Heart failure literature has demonstrated the importance of specific education to facilitate self-care and management. A review of 35 educational intervention studies in heart failure found that disease-state knowledge, self-monitoring, medication adherence, time to hospitalization, and days in the hospital improved with patient education.[15] Similarly, PH patients need to learn how to monitor and report their symptoms and weight fluctuations, restrict sodium and fluid intake, adhere to medication regimens, and maintain physical activity. Clearly, education prior to discharge reduces readmissions and associated health care cost.[16] Nurses and allied health personnel are critical to the success of patient education.

Discharge planning and education for the PH patient should be multidisciplinary and may include cardiologists or pulmonologists, advanced practice providers, nurses, pharmacists, social workers, physical and occupational therapists, specialty pharmacy staff, and discharge planners. It is crucial to clearly define the roles that each team member will play in the patient's care. There should be a plan for close communication with members of the outpatient PH team. For patients who have initiated new PH-specific medications, discharge planning should include completion of insurance prior authorization and approval, documentation of copay amount and affordability, referral and acceptance for copay assistance programs, and identifying a specific outpatient pharmacy to provide the medication immediately upon discharge. This will avoid inadvertent discontinuation of PH-targeted medications after discharge, which can lead to clinical worsening and rehospitalization.

The development of discharge education checklists, teach-back materials, hospital television videos, and written take-home materials may be useful to support educational efforts. Implementing a process to incorporate appropriate amounts of teaching on a daily basis may affect the patient's ability to manage their disease more independently. Hospital discharge instructions should include standard PH-specific instructions for symptom management and contacting the outpatient PH care team. Ideally, these discharge plans are delivered to the patient by a member of the PH care team or a bedside nurse with PH expertise and training.

Psychosocial factors may also affect PH hospital readmission rates, as has been demonstrated in the heart failure population. Low health-related quality of life has been shown to be a predictor of readmission, and this may be similar in a PH population.[17] Review of the PAH literature demonstrates depression rates of 7.5% to 53% and anxiety and panic disorder rates of 19% to 51%.[18] In fact, PH-specific patient-reported outcome tools have been increasingly used in various settings and may be incorporated into hospital discharge workflow, posthospitalization follow-up visits, routine outpatient appointments, and hospitalizations to guide education and treatment. Recent European Society of Cardiology recommendations include psychological support for PH patients as a class I recommendation.[19] In general, patients with depression are less likely to adhere to medication regimens and lifestyle modifications, which may increase risk for hospital readmission. While addressing acute medical illnesses takes precedence during hospitalization, consideration for assessment of depression should be considered. Screening for depression is an important component of care planning, and nurses may be best suited to facilitate screening and potential interventions. While numerous tools exist for depression screening, each institution may provide guidance on a preferred screening method. Similar to patient education, a multidisciplinary approach to depression intervention is recommended. A basic understanding of depression is necessary for nurses to understand its effect on adherence to treatment and contributions to hospitalization. Nurses are able to support patients and families to alleviate symptoms and educate on the importance of social support after discharge. Given a paucity of data on treatment approaches for depression in PH, methods used

in other chronic illnesses have been suggested, including relaxation training, breathing techniques, and cognitive behavioral therapy.[18] Without question, mood disorders are underdiagnosed in PH, and the impact on overall morbidity and mortality are not understood.

TRANSITIONAL CARE AND FOLLOW UP

Multidisciplinary planning for transition from inpatient to outpatient setting is imperative. Coordination and collaboration between settings is critical to improve patient outcomes and reduce readmissions. Transitional care programs include patient and family education, telephone follow up, early clinic follow up with early reassessment of medications and clinical status, while including caregivers and postdischarge providers.[13] Successful transitional care in heart failure patients included 8 common themes: planning for discharge; multiprofessional teamwork, communication, and collaboration; timely, clear, and organized information; medication reconciliation and adherence; engaging social and community support groups; monitoring and managing signs and symptoms after discharge; and delivering patient education, outpatient follow up, advanced-care planning, and palliative and end-of-life care.[20] Home nursing visits, nursing case management including structured telephone support, and follow up in specific disease management clinics have been shown to decrease readmissions compared with usual care.[16]

Structured telephone follow up after hospital discharge by a nurse clinician is a simple, cost-effective method of assessing patient status and wellbeing, reviewing key discharge education and instructions, and identifying issues that may lead to poor outcomes.[21] This may address numerous concerns in a high-risk population and should be implemented ideally within 48 hours of discharge. Studies demonstrate telephonic intervention has the greatest impact on avoiding readmission when implemented as close to discharge date as possible.[20] The initial phone call may include determining whether prescriptions have been filled appropriately, durable medical equipment has been obtained, daily monitoring is occurring, disease and symptom management education may be reviewed, and any adverse events can be identified and reported to PH providers. Education regarding the purposes of each medication, dose adjustments and frequency, and how to take them appropriately are important basic areas essential to patient self-management. Consideration of a posthospital discharge telephone checklist such as the "Pulmonary Hypertension Posthospital Discharge Telephone Checklist" (Appendix 1, courtesy of the University of Michigan Pulmonary Hypertension Program) may be valuable to ensure comprehensive, consistent assessment. Ideally, a member from the PH program team completes this checklist. The length of hospital stay, acuity on admission, comorbidity, and emergency department visits (LACE) risk score identifies patients that are at risk for readmission or death within 30 days of discharge.[22] The PH nurse is critical in teaching patients when to contact the office related to worsening of PH symptoms. Educating PH patients and providing written information regarding "When to Call Your Doctor" (Appendix 2, courtesy of the University of Michigan Pulmonary Hypertension Program) may serve as a proactive tool to reduce need for hospitalization.

Posthospitalization follow-up clinic visits or virtual video visits may be instituted within 2 weeks of discharge. Similar to initial telephone follow up, overall disease, symptom, and medication education may be provided, while assessing clinical condition and any adverse events. Self-management strategies can be reinforced to patient and family, and consideration for additional physical and psychosocial support may be addressed. Prompt hospital discharge follow up has been linked with decreased rehospitalization rates, emergency department use, and death.[23]

Palliative care may be offered simultaneously with disease-oriented care to support chronic symptom management and improve quality of life for patients and families with PH. Palliative care has been demonstrated to improve communication among patient, family, and provider as it forces open discussions about disease, therapeutic challenges, and patient wishes.[24] Palliative care may be underused in PH as the need is often not recognized by health care providers and may be considered much earlier in the disease trajectory to provide additional support.

Of note, PH patients may not be able to maintain employment due to chronic symptoms and lifelong illness, necessitating Social Security Disability status, affecting income and resources. As is understood in heart failure patients, those with lower socioeconomic status may be at higher rates of acute heart failure readmission, possibly related to low income and literacy rates, lack of insurance and social support, and substance abuse, which affect self-management.[25] These factors may also be considered higher risk findings in the PH population, as these patients may have increased likelihood to experience high readmission rates, consume high levels of resources, and may overuse emergency department visits, resulting in more fragmented health care.

CONCLUSIONS

The hospital discharge process is a complex, multifaceted plan that should begin on the first day of admission. Just as standardized treatment protocols can improve patient outcomes, a similar plan for multidisciplinary discharge planning may enhance safe transition from hospital to home. Daily teaching provides an opportunity to assess information carried over and accurate understanding of treatment plans, as well as to review changes in care plans that may be evolving during a hospitalization. Use of checklists and documentation of patient education may be useful. Prevention of PH rehospitalization may improve patient outcomes and reduce health care system financial burden. Further study is warranted to elucidate PH patient–specific factors and interventions that may reduce rehospitalization rates.

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APPENDIX 1.

Pulmonary Hypertension (PH) Posthospital Discharge Telephone Checklist (To Be Completed With Patient and Caregiver)

1. Assess overall status:
   a. Better, worse, or same since discharge? Consider for all patients and especially those with high LACE scores.[a]
2. Assess patient's home care:
   a. Is the patient receiving any care at home (nursing, PT/OT, other)?
   b. What is the phone number for organization?
3. Discuss home arrangements:
   a. Are arrangements made at job?
   b. Are arrangements made for caregiver support?
4. Review any follow-up appointments:
   a. When are the next appointments (primary care physician [PCP], referrals to other specialists, pulmonary rehabilitation, etc.)?
5. Consider contacting PCP with discharge plan and instructions for continuity.
6. Discuss home medical equipment:
   a. Did the patient receive any necessary equipment, oxygen, walker, hospital bed, bedside commode, other?
   b. What is the phone number for provider?
7. Assess high-risk symptoms:
   a. Explain potential symptoms, how to monitor, what to expect while at home, who to call during office hours and afterwards, and under what circumstances patient should visit the emergency department.
8. Assess medications:
   a. Review list of all medications including dose, frequency, over-the-counter and herbal supplements.
   b. Review name and phone number of who to call for questions.
   c. Review new medications or changes in dosage thoroughly. Have new prescriptions been obtained? Any concerns with new prescriptions or cost?

9. Review self-management strategies:
    a. Review daily weight monitoring (how it should be done, how to record, etc.).
    b. Review dietary restrictions, exercise recommendations, etc.
10. Provide teach-back as appropriate.[b]
11. If necessary, arrange outpatient investigations (laboratory, radiology, etc.).
12. Develop method to obtain information from postdischarge providers (PCP, in-home clinical support, specialty pharmacy, other).
13. Assess for signs of stress and depression, including patient and caregiver.
    a. Review psychosocial resources such as social work, support groups, PH peer mentors, recommended online support groups, and contact information.
14. Review recommended online resources, such as phassociation.org and phaware.org, and organizations that may provide financial support for medication access.

[a]LACE index is a score calculated based on 4 factors: (L) length of hospital stay, (A) acuity on admission, (C) comorbidity, and (E) emergency department visits. A score of 10+ indicates high risk for readmission to hospital.

[b]Teach-back is the process of explaining information to patients and asking them to restate the information to assess accuracy. The instructor then repeats the process until the patient demonstrates correct recall and comprehension.

APPENDIX 2.
Pulmonary Hypertension (PH) Program: "When to Call Your Doctor"

Call 911 for:

- Severe shortness of breath.
- Loss of consciousness (pass out).

Contact the PH program staff for any of the following:

- You experience a weight gain of 2 pounds in 1 day or 3 pounds in 3 days.
- You develop new or increasing swelling of the legs, feet, or abdomen.
- You develop new or increasing shortness of breath that lasts for more than 3 days.
- You experience unusually high or low urine output.
- You experience a "blackout spell" or an episode of lightheadedness.
- You experience an increase in overall fatigue.
- You develop new or increasing palpitations or heart fluttering.
- You have uncertainty or questions regarding your PH medication.
- You develop new or worsening side effects from your PH medication.
- You develop signs of a central line infection.
- You change your insurance or cannot get your PH medications.

Contact your primary care physician when:

- You have symptoms of upper respiratory or other infection.
- You need refills or have questions regarding non-PH medications.

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