Pediatric Pulmonary Hypertension Guidelines Highlights and Challenges

Guest editors Usha Krishnan, MD, DM, and Dunbar Ivy, MD, led a discussion among physicians regarding the development and implementation by clinicians of the pediatric pulmonary hypertension guidelines. Participating in the conversation were Eric Austin, MD, Director of the Pediatric Pulmonary Hypertension Clinic and Assistant Professor of Pediatrics in the Division of Allergy, Immunology, and Pulmonary Medicine at Vanderbilt University Medical Center, Nashville; Jeffrey Fineman, MD, Division Chief of Pediatric Critical Care and Director, Pediatric Pulmonary Hypertension Service at the University of California, San Francisco; Ian Adatia, MBBS, MD, Director of the Pulmonary Hypertension Clinic at the Stollery Children's Hospital, Edmonton, Alberta; Erika Berman-Rosenzweig, MD, Medical Director of the Pulmonary Hypertension Comprehensive Care Center and Associate Chief of Pediatric Cardiology at Columbia University Medical Center of New York Presbyterian Hospital, New York; and Steve Abman, MD, Professor of Pediatrics in the Division of Pediatric Pulmonary Medicine at the University of Colorado Denver and Children's Hospital Colorado.

Dr Ivy: This issue of *Advances in Pulmonary Hypertension* is on pediatric PH. We have had 2 prior issues on pediatrics, but this one in particular we were very excited about, because of the recently published pediatric PH guidelines, so most of the articles in this issue relate to specific topic in the area of pediatric pulmonary hypertension; We've asked authors to tie into the guidelines and highlight the parts of the guidelines relating to their area of particular expertise. So, I would like to begin by asking Steve Abman to give us a brief introduction to the development of the guidelines, the challenges of the guidelines.

Dr Abman: The Pediatric Pulmonary Hypertension Guidelines were designed by an interdisciplinary team comprised of members with diverse multidisciplinary backgrounds including pediatric cardiology, neonatology, pediatric pulmonary, critical care, and others. This is important since historically, many of the children with diverse diseases associated with pediatric pulmonary hypertension are often followed primarily by different disciplines in isolation. The experience over time has been that the best care can be provided by teams at medical centers with different backgrounds that could interact with regularity, which will enhance long-term outcomes of children in these diverse settings. In addition, approaches to the evaluation and management of childhood PH can differ among sites, with little sense of what are the optimal strategies. As such, the guidelines were developed, because there really wasn't a starting point for us as a community to really get together and see where we're currently at as a starting point in the field. This includes how we define pulmonary hypertension in children; what kind of diagnostic evaluations we perform; what drugs we use to treat neonates, infants and older children; and what other non-pharmacologic strategies can be applied in different specific diseases associated with pulmonary hypertension. With the support and guidance of the American Heart Association and American Thoracic Society, we met as a group over a 3-4 year period. We followed precise rules for grading the literature and available data, had extensive discussions, wrote the results of our work as subgroups and prioritized our recommendations for presentation as a guidelines document. So, the whole process took quite a bit of work from a number of hard-working team members who put the guidelines together, and we're excited about the product and their early impact. Most importantly, we recognize that a big role of the guidelines is to help highlight where the gaps in our current knowledge are, and hopefully, have this document have a favorable influence on leading priorities for future clinical research in these different settings of childhood PH.

Dr Ivy: So, I'm curious if the other authors could describe what they feel has been beneficial to their practice about the guidelines and maybe what gaps they see in those areas.

Dr Fineman: Well, I think my experience with the guidelines has been most positive with interacting with referring caregivers. I think that there's a lot of people that are kind of taking care of patients--one or two--and don't necessarily feel comfortable and the guidelines have been very helpful for them to not only help them care for patients, but also to seek out advice from others. I think, for me, that's been the most notable thing is how widely read they've been by people that have some PH patients as part of their practice, and how helpful it's been for them to not necessarily guide therapy, but at least guide their questions as to what to do next.

Dr Krishnan: Ian, do you have the same experience in your practice?

Dr Adatia: Yes. Yes, I agree with Jeff. I have heard that the guidelines are very helpful for physicians who see the occasional patient with PH, especially as an outpatient.

Dr Krishnan: Eric, did you find the guidelines to be useful in your armamentarium when dealing with an acute patient consult?

Dr Austin: Absolutely. I I find that the guidelines are particularly helpful to pro-

vide support for the assessments and recommendations that we make during our inpatient consultations in the neonatl and pediatric ICUs, in particular. We have a number of fantastic clinicians who I work with who've been doing cardiopulmonary related disease care for a long time, but having a published guideline to Share creates a mechanism to both eeucage and give justification for our approaches in the care of the complex child.

Dr Ivy: Most of the recommendations are based mainly on our clinical expertise and experience and not based on randomized trials as in adults. Have you seen any pushback from clinicians or others asking for more evidence-based guidelines?

Dr Rosenzweig: I think that's a great point Dunbar. This is really a landmark starting point for the pediatric pulmonary hypertension community even with the limitations in terms of randomized clinical trials in children with PH. I believethere is tremendous value in having this type of document and guidance from a group of experts that have a large collective experience in managing pediatric patients with pulmonary hypertension. My impression is that it has been a welcome tool for practitioners that we work with. That said, we always can strive to do better. Given the limitations with regard to the paucity of data from clinical trials, it is clear that we need more research to direct some of these recommendations and strengthen the foundation of these guidelines, specifically with regard to medical therapies.

Dr Austin: I would agree with that entirely and also say that it has really laid the groundwork for our colleagues to understand why it's sometimes difficult to provide clearly justified recommendations concerning some of the issues around our patients with pulmonary hypertensive vascular disease. The guidelines do a very nice job of highlighting our tremendous need for further studies that ideally will proceed in a collaborative manner across many centers.

Dr Krishnan: When you were getting together as a guidelines writing group, were there major differences in any of the management plans between different institutions or were people mostly in agreement?

Dr Ivy: There was active discussion about some of the recommendations, in particular the way patients with bronchopulmonary dysplasia are managed. I think also there was some active discussion on premature babies with PPHN physiology and the use of inhaled nitric oxide.

Dr Krishnan: Great. I think this brings a beautiful segue since the words bronchopulmonary dysplasia were mentioned. Dunbar and I were discussing that we wanted to highlight some of the issues with that. So, one of the questions we had was regarding timing of cardiac catheterization and what measurements/ procedures/imaging do you include in a typical BPD patient undergoing cardiac catheterization?

Dr Adatia: I delay cardiac catheterization if they have a good quality echocardiogram and contrast CT scan that shows the pulmonary veins well, absence of aortopulmonary collaterals, and no peripheral PS or PDA. It is not always so straightforward to put them through a cardiac catheterization especially if they are very small or have just weaned from invasive ventilator support. However, if they are not responding to oral therapy or if there's something that needs to be explained or assessed in more detail like a cardiac shunt,then we pursue cardiac catheterization. In the absence of those things, if it's straightforward BPD without pulmonary vein stenosis or a shunt, you've got a good quality echocardiogram and CT scan, then I wait, and make sure that all their ventilation requirements are taken care of with attention to reflux, optimizing blood gasses with noninvasive ventilation and support. I like to make sure that pulmonology and ENT services have evaluated them. The CT is also good for assessing the airways and lung parenchyma We've seen a number of BPD babies with PH or spells who've actually had problems with their airway either subglottic stenosis, unanticipated vocal cord paresis, distal tracheal stenosis. As far as the cardiac catheterization is concerned, I follow our usual routine with vasoreactivity testing to iNO and hyperoxia. Sometimes in the BPD babies I find that you catheterize them and with their airway and ventilator requirements supported and with them settled under anesthesia, the PA pressures are really not very elevated and even the RV or the pulmonary artery-to-systemic ratio is not that high either. I'll sometimes stimulate PH to mimic what might happen on the NICU when the baby gets upset or the CO_2 goes up. So, depending on the stability of the baby, I may let the CO_2 come up or the saturations decrease by weaning the baseline FiO_2 requirement in a controlled way and monitor the PA pressures. I think this provides useful information if there is discord between the catheter results and the clinical impression on the NICU. I've seen a couple of children with increased CO_2 causing PH and that increased PH has been blunted by sildenafil.

Dr Ivy: So, Ian you're suggesting that you find CT in the BPD patient very beneficial. Is your general protocol then to do a CT angio before starting sildenafil in a BPD? Other centers wait do to a cath until more than sildenafil is needed.

Dr Adatia: I do a CT angio before starting any therapy, because I think it gives you a good impression of the lung disease as well, especially if the clinical estimation of the lung disease doesn't match what's going on with the baby on the NICU. I like to know all the things that I mentioned before on the CT scan before starting therapy--especially pulmonary vein stenosis. I always take into account the stability of the baby, but we can get a contrast CT done very quickly with just a couple of minutes' scan time. So it is practical with good risk/benefit ratio, even for a baby that's only recently been extubated.

Dr Ivy: Usha, what is your decision tree then for BPD with PH and use of CT versus cath?

Dr Krishnan: Well, I don't do a cardiac catheterization on them when they're

very sick or when they're very little. So, I agree with Ian. We have been getting more CTs to look at collaterals, PDA, pulmonary veins, any other lung abnormalities that we didn't pick up. Of course, the airways are very important, especially in Down syndrome babies and other premature babies with broncho- or tracheomalacia, because they seem to get even more affected when we start pulmonary vasodilators, but I would tend to cath especially before adding prostanoids. In an older child, say a 6-month-old who comes back with pulmonary hypertension when they didn't have it before, I would perform a hemodynamic study before starting medications, if possible.. We've had several infants who even went home from the NICU and then came back. So, in those I would tend to cath them so as to not miss something, and also to make sure their wedge pressures and LV end diastolic pressures are okay.

In that aspect, I was just wondering what people did with pulmonary vasodilator testing in these babies and do they routinely perform angiograms and left heart cath?

Dr Abman: Before we discuss cardiac catheterizations and acute vasoreactivity testing, I just want to reiterate what Ian was saying and Usha as well. Long before we think about cath to evaluate PH identified by echocardiogram, we need to first consider the impact of current ventilator and respiratory management. Although targeting blood gas values and oxygen saturations are an important part of this process, targeting FRC and lung volumes plays a key role in optimizing PH management. In many preterm infants with established BPD who have pulmonary hypertension, optimizing lung recruitment and volumes and minimizing gas trapping or regional atelectasis has a huge impact on pulmonary hemodynamics, even beyond the effects of PH-specific drugs. Understanding airway structure and physiology, as Ian mentioned, with bronchoscopies to look for tracheo- or bronchomalacia and other airway lesions, optimizing ventilation and lung volumes by adjusting tidal volumes, inspiratory times, PEEP, and rate in ways that are not quite traditional for acute respiratory failure or ARDS is often required and beneficial. Sometimes some of the best interventions we could do for PH in these kids--long before treating them with PH-specific drugs--is to optimize respiratory care, which plays a big part of our PH service consultation. We think that this approach (that is, rigorous evaluation and treatment of underlying lung disease) must precede a trip to the cath lab or the initiation of PH drug therapy. This is a major highlight in the guidelines so that one does not simply see evidence of PH by echo and start a drug; but rather, first take a step back and re-evaluate what's going on with the chronic lung disease management.

Dr Rosenzweig: I totally agree with that, and I think that's extremely important to highlight: the cardiac catheterization should try to mimic a stable steady state for the child with PH even if under anesthesia. If you haven't optimized with conservative management first, including avoiding triggers of pulmonary hypertension--for example, respiratory acidosis and hypoxia-- then you're not going to get accurate numbers, and you can potentially do more harm than good. I think one also has to understand that having a child under general anesthesia to do the procedure may not always reflect the hemodynamics of a child who is awake and active.

Dr Austin: I agree wholeheartedly. Comorbid conditions are so important to address. With specific regard to the question about acute vasoreactivity testing in the BPD population: with our initial cardiac catheterization, in the cases for which we do get to that point, we use the same approach that we would use for our primary pulmonary hypertension or Group 1 PH assessments and evaluations over time. That is, we will try to get them to room air if it's safe and appropriate for the initial phase of testing (or to whatever minimum level of oxygen that would be appropriate at the time of hemodynamic testing). We would then use 100% FIO_2 and then we would use 100% FIO_2 plus 40 ppm in the traditional approach. As Ian alluded to, we will at times do some manipulations thereafter if we want to try to evoke a response, but that is less common. While each case is different, when it's safe we generally try to proceed with cardiac catheterization before adding a second PH-specific therapeutic agent.

Dr Abman: I think what we try to emphasize in the guidelines is that centers with strong PH programs have extensive experience with these young infants with severe disease and are evaluating them in the cath lab and doing everything that Eric just mentioned. However, other centers are very uncomfortable with some of these approaches, and may have limited experience. So, we try to encourage consultation and referral to programs that have strong PH care experience to enhance benefit/risk ratios for evaluations and interventions, especially related to cardiac catheterization or initiation of some therapies. We emphasize the importance working with experienced pediatric hypertension centers with interdisciplinary programs.

Dr Rosenzweig: And I think that's a very important point with regards to these guidelines. They definitely can open the dialogue and give guidance, but if there is a procedure that a center is uncomfortable doing, I would hope this dialogue would also encourage a partnership with major centers that have the expertise in handling the highly complex child.

Dr Abman: Along the lines of our discussions regarding preterm infants with PH and the points that Dunbar raised, our statements in the guidelines help clarify the potential role for nitric oxide . One of the issues that we were concerned about is that although inhaled nitric oxide is not recommend for the prevention of chronic lung disease in premature infants, sometimes that is translated by some neonatologists to mean that inhaled nitric oxide should not be used in preemies at all, even in acutely ill preterm infants who have extra-pulmonary shunting with documented PPHN physiology, especially in the setting of oligohydramnios or prolonged rupture of membrane and elements of lung hypoplasia. We tried to clarify

that picture because the data, even if based on several case series and not on multicenter randomized trials, strongly support favorable responses to inhaled NO in this setting without significant toxicities. As a group, we have encouraged this approach toward the management of severe PH in acute respiratory distress even in preterm infants, which will hopefully provide some help and advice for neonatologists who read this.

Dr Krishnan: Great. So, one of the questions that I have been asked from neonatologists--basically based on the guidelines--is the use of calcium channel blockers where we have come out with a statement that would use them beyond the age of 1 year, and the neonatologists state that they use calcium channel blockers all the time in their systemic hypertensive patients. Any thoughts or comments on this?

Dr Ivy: It's a very good question. There was active discussion during the development of the guidelines on timing for use of calcium channel blockers in neonatal and infant PH. The agents have been used for systemic hypertension in infants, but there is little data on use in PH. We voted for the recommendation to use CCBs over 1 year due to a potential safety issue. If a different group had met, they might have said that there is no age restriction.

Dr Adatia: , I think it's an interesting question. There are 2 considerations from my point of view. One is that it's very different using a calcium channel blocker in a patient with systemic hypertension and one who has pulmonary hypertension. I think the risk/benefit is different, and I've seen low cardiac output severe enough to require intubation and resuscitation in infants who had an arrhythmia and were treated with a calcium channel blocker. So, I think that's been where my concern comes even though I acknowledge that the type of calcium channel blocker used for arrhythmias is different. The other concern is that I think very few infants with pulmonary hypertension are calcium channel blocker candidates based on strict Sitbon criteria or the criteria described by Moledina in the UK registry. As you all know, there are very specific indicators for the use of calcium channel blockers in pulmonary hypertension, and patients with BPD don't quite follow those criteria in my experience. Also, to get that information you'd have to catheterize them way up front. So, I guess that's where my wariness comes in.

Dr Abman: I really agree with exactly what Ian said, and past studies of the acute response of BPD infants to calcium channel blockers in particular showed that the response to giving supplemental oxygen to correct hypoxemia was as effective as the impact of acute calcium channel blockade. In other words, removing the hypoxic stimulus had as much effect on lowering pulmonary artery pressure as acute calcium channel blocker treatment. In addition, from Dunbar's cath data, we compared the acute response to oxygen, inhaled NO, and calcium channel blockade in some slightly older infants with BPD with PH, and reported that these subjects who were responsive to oxygen and nitric oxide failed to have an acute response to calcium channel blockade.

Dr Rosenzweig: I do want to acknowledge that there definitely was a discussion around the use of calcium channel blockade in young infants among the panelists. But, there was very little experience using it in young infants successfully within the group. I would welcome further investigation of this particular guideline in the future for the non-BPD patients; I would ask this roundtable panel a similar question if they have had any young patients, less than 1-year-of-age, but let's say robustly responsive to nitric oxide, who they have treated with a calcium channel blocker. We have had a couple probably over 3-months-of-age that we have treated with calcium channel blockades with a very good response. Anyone else with that experience?

Dr Abman: I agree with Erika. In the past, we would generally use only oxygen, diuretics, and digoxin, and then add a calcium channel blocker; but this was an era of particularly high mortality. Management has clearly changed in many ways, and the availability of PH-specific medications has dramatically changed our approaches. We can certainly challenge the ideas in the guidelines, especially regarding CCB use. We emphasize the importance of getting more data on this experience from which we can change recommendations for future guidelines. Regarding the current recommendations, not everyone was uniform on defining their role in current management, but we reported the overall consensus that led to the grading and scoring of the evidence in the guidelines.

Dr Adatia: I would agree. I don't think I've seen any patients in the last 6 years who were under a year with IPAH who had normalized their PA pressures with inhaled NO. So, for me, it hasn't been an issue.

Dr Rosenzweig: Again, I would not consider it for a BPD patient, but I have been able to use it successfully in a few non-BPD infants who eventually went on to receive other therapies, as well.

Dr Krishnan: While on the subject of cardiac catheterization, the other question is have people found elevated LVED pressures making you change your treatment practice as far as pulmonary vasodilators?

Dr Ivy: We have seen a handful with elevated LVEPD and have used gentle diuresis and afterload reduction in them.

Dr Abman: I agree with Dunbar, We've had cases where a patient's pulmonary hypertension per se was not that striking, but the presence of high diuretic requirements for managing their chronic lung disease and recurrent respiratory exacerbations were very striking, Some of these infants have LV diastolic dysfunction. If one looks the data from the Spanish registry, which was based on a highly selective population who are selected for catheterization, 54% of them had elevated LVEDPs or estimates of left-sided pressures, so I think it's really an important topic to highlight. During catheterization, in cases where one unmasks a pulmonary occlusion pressure

that's on the high side, a small volume infusion as used more commonly by our adult colleagues to evaluate the impact of left heart disease, should be used more often in kids. The other thing we emphasized in the guidelines along these lines is to not forget about the congenital diaphragmatic hernia (CDH) population, where we think LV dysfunction from either underdevelopment, diastolic dysfunction, or other factors can contribute to the clinical course, and should be especially suspected in sicker patients who are not responding well to vasodilator therapy. So, I think not forgetting the left ventricle ends up being something that we tried to highlight in the guidelines as well.

Dr Krishnan: Right. So, I wanted to poll the group's experience on connective tissue-related pulmonary hypertension, because there's not so much discussion about it anywhere, and I wanted to see what people thought, what they found, conditions. Jeff?

Dr Fineman: We haven't had much experience seeingthe more classic connective tissue disorders and having pulmonary hypertension. We've screened a few, but we really haven't seen a high incidence at all. We've had a couple patients that referred to our neurosurgeons that ended up having pulmonary hypertension, but in terms of the classic connective tissue disorders, we really haven't had much experience with it.

Dr Abman: As with all rare diseases, data are limited on the management of PH in that setting of collagen vascular diseases. Many questions persist as to whether we can do better with specific rheumatologic or anti-inflammatory strategies along with PH-specific drug therapy and how to optimize care, yet I don't think many of us have sufficient experience with some of the variability in course. That's where having networks of interactive PH programs can help pool the numbers and hopefully lead to greater understanding of our current experience together and lead to more optimal design of interventional studies.

Dr Krishnan: I think APAH-CTD might be an uncommon, and perhaps underdiagnosed condition, but Erika and I have seen quite a few. Erika, would you like to talk about it?

Dr Rosenzweig: We certainly have a large experience with adult connective tissue diseases in the field and pulmonary hypertension, but clearly less so in children. I agree with reactivity component particularly with lupus patients. Eric had mentioned that sometimes just treating their underlying lupus if they are having a flare will improve the PH. We have found that some of our lupus patients are the best responders to targeted medical treatment for PH, and some of these patients do really well in between any kind of lupus flares. On the flip side, however, they can get sick quite quickly during a rheumatologic flare. With regard to other connective tissue disorders like scleroderma, the teenagers that I've seen have mostly been associated with severe lung fibrosis and act more like a Group 3 PH patient. We've also had some other interesting cases with macrophage activation syndrome that I think Usha was referring to.

Dr Krishnan: Right, and we have found that when they have their PH flares, sometimes the PH flare precedes their rheumatologic flare. So, they come in with a PH crisis, and a week or so later, their rheumatologic biomarkers rapidly increase, and they actually respond to treatment with Anakinra and like medications for their rheumatologic conditions, and then everything settles down. So, when they do come in with flare of one or the other, we get both teams actively involved with them, and try to manage the inflammation as quickly as possible while supporting their PH. We have seen PH with mixed connective tissue disease, JIA, SLE, systemic sclerosis, and with macrophage activation syndrome.

Dr Ivy: We have a small case series of several patients that presented with pulmonary hypertension and a strong family history of connective tissue disease, and then after years went on to develop positive antibodies, and either lupus or mixed connective tissue disease. So, it was interesting that they presented more with PH than they did with classic signs and symptoms of connective tissue disease.

Dr Rosenzweig: Dunbar, that's a really good point, because we will still send screening labs for rheumatologic disorders serially after diagnosis for many years even after the diagnosis of let's say idiopathic PAH, because a connective tissue disorder could emerge later in the disease course. So we still screen the kids periodically as they grow up for rheumatologic disorders even if they're not manifesting them clinically.

Dr Austin: I'd say as somebody who was less involved in the guidelines than you all, it's an incredibly valuable document to the field and is important for all of us. It sets the stage for the next 5 years and beyond.

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