# • Identifying the Complex Spectrum of Childhood PAH
# • Selecting Candidates for Aggressive Treatment

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**Dr Rosenzweig:** In this roundtable we will be discussing pediatric pulmonary hypertension, including current considerations and strategies for the management of childhood pulmonary hypertension. We are fortunate to have some very experienced physicians in the field of pediatric pulmonary hypertension for this discussion. Children are often treated as "small adults," which we know is not always the case. And, while there are many similarities, there are also inherent differences in terms of etiology, natural history, and the treatment of pulmonary hypertension in children.

Let's start by discussing some of the major differences or challenges that we often encounter in practice when dealing with a new child who presents with idiopathic pulmonary arterial hypertension for the first time, when compared to an adult. Dr Ivy, how do you assess severity of disease in children? Are there additional considerations in selecting treatment in a child as opposed to an adult patient?

## Confirming the Diagnosis

**Dr Ivy:** In all cases of pulmonary hypertension, it is important to establish a definitive diagnosis before considering treatment. For many pediatric diseases, there is a single unifying cause of disease. This is not always true for pulmonary hypertension in children. In patients presenting with severe pulmonary hypertension, it's very important to look for the other causes of pulmonary hypertension and not just assume that it is idiopathic. For example, we would perform a comprehensive evaluation looking for congenital heart disease, lung disease, liver disease, hematologic disease, connective tissue disease, and thyroid disease. Our routine evaluation for severe pulmonary hypertension includes blood evaluation, sleep study, and a chest CT. Approximately 5% of the children who are considered to have idiopathic disease have other associated abnormalities, such as hyperthyroidism, hypothyroidism, a coagulation abnormality, or abnormalities of lung function.

Therefore, it's important to look for those other causes and to treat any possible causes that may be apparent. We perform cardiac catheterization in all children with severe pulmonary hypertension to look for other causes and obviously to perform a vasoreactivity trial, including use of inhaled nitric oxide to determine reactivity. In patients who are reactive with near normalization of pulmonary artery pressure, we consider a trial of calcium channel blockers. I no longer take children back to the ICU with a Swan-Ganz catheter in place and then dose them with calcium channel blockers because of the difficulties of maintaining the line. That would be one difference between children and adults.

**Dr Haworth:** The diagnostic pathway is not too dissimilar in adults and children but it is essential to make absolutely certain that you have the complete diagnosis. I think that's mandatory. The likelihood of a positive vasodilator response in children is not very high, in my experience. Reports vary as to how often we see a really robust positive response in children as compared with adults. In my experience, and my experience isn't too different from the adult experience now current, the number of positive responders is small. The number of true positive responders of true idiopathic pulmonary arterial hypertension, whether or not you've identified the gene mutation, is small.

**Dr Ivy:** I agree. Erika, in one of your papers you had published that 40% of children may show adequate vasoreactivity to be treated with calcium channel blockers. More recently, our paper together on use of bosentan in children suggested that only 20% of those patients were acute responders.

**Dr Rosenzweig:** That is correct.

**Dr Ivy:** So it may be even lower than we had previously thought.

**Dr Haworth:** I think it is low. But part of it is that you have to be very careful about the definition of a positive responder.

**Dr Rosenzweig:** I agree.

**Dr Haworth:** And you have to see "responsiveness" in a historical context because it's not so long ago that we had only calcium channel blockers with which to treat our patients. At that time the definition of a positive responder was someone who had a fall in pulmonary arterial pressure and/or vascular resistance of 20% with no fall in cardiac output. But any of us who have had experience in pulmonary vascular disease, and in correlating the pathology to the catheterization findings, know that's not perhaps the best way to go about clarifying the problem. If you have a starting resistance of let's say 50 units per $m^2$ and you get a 20% fall in pressure/resistance, that still leaves you with a high resistance indicating terrible pulmonary vascular disease that is not going to respond to a calcium channel blocker. So, I think that our definition of a positive responder has been, if you like, defined and redefined over the years and we now realize that if you don't get a drop in the pulmonary arterial pressure or vascular resistance, not necessarily to normal, but to a near normal level, then you're either going to fail with a calcium channel blocker or have a very temporary success, which is really quite dangerous. You've got to be very secure in that you really do have a positive responder before you plan what you hope will be long-term administration of a calcium channel blocker only.

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**Dr Rosenzweig:** Yes, and do you routinely restudy them?

**Dr Haworth:** Any patients I treat with a calcium channel blocker will be routinely restudied, and because I've been very strict in my definition of a positive responder, the patients have stayed positive responders.

**Dr Rosenzweig:** That's an important point. Do you think we rely more on hemodynamic data for children because it's more difficult to assess their exercise capacity and grade the severity of their disease?

**Dr Abman:** That's a good point. Naturally, the quality-of-life scales and 6-minute walk tests, which have been critical end points for determining efficacy in adult patients, can be applied only selectively to older children We don't have an equivalent 6-minute "crawl test" or some functional assessment beyond hemodynamics and oxygenation for infants and young children yet.

**Dr Haworth:** It is more difficult in a way. But I don't think you have to be terribly expert to see whether a child is thriving or not. And one of the things I think is very interesting, if you do a catheterization that confirms your clinical impression that things are not good, how might those catheterization findings influence your management? The extent to which catheterization data influence your management after the first catheterization depends on the medication the child is receiving. Once the patient is receiving maximal therapy, I don't routinely recatheterize. Because what else can one do? If the child is receiving a calcium channel blocker, or perhaps sildenafil or bosentan, then there's a very good case for checking by recatheterizing because there are other things you can add that would be extremely beneficial.

**Dr Rosenzweig:** What do you do when you have a parent who thinks the child is better but the. . .

**Dr Haworth:** Oh, but they all do—until the child is terribly sick. That's our difficulty as physicians, because if you had a very sick child with an incurable disease, you would be looking for the positive. I think that's natural.

**Dr Rosenzweig:** In terms of our treatment approach for children the philosophy initially had been to be most aggressive in using intravenous prostacyclin. Now that there are some other agents available, has that philosophy changed in terms of now deferring intravenous therapy and using other oral agents as first line therapy?

**Dr Haworth:** No. That's an extremely important point because there are other agents that it is tempting to use when the child is not terribly symptomatic. But if at cardiac catheterization the pressures and resistances are really very high and you have a growing child who is remodeling his or her entire body, including the lung and pulmonary circulation, then it's very tempting to go for an aggressive therapy because if you're ever going to stabilize that child, let alone even think about remodeling, it's going to be during the early phase. Not necessarily the early phase of the disease, but the early phase of the child's life. I think the question you've asked is a very important and relevant one, and one to which we don't know the answer.

**Dr Ivy:** Generally I would agree. In the younger child who presents with severe disease, I'm actually very aggressive. Some of our best long-term responders have been younger children who have severe disease whom we treat with intravenous epoprostenol. Those are the patients who seem to be more likely to have a lower pulmonary pressure either years or a decade later. The patients in this small group are those who may be

able to transition off intravenous therapy and be maintained with an oral therapy.

**Dr Haworth:** Yes, but then I think you need to be very cautious about the diagnosis. I think it must be very rare to have a rip-roaring young idiopathic pulmonary arterial hypertension patient taken off epoprostenol successfully. These patients are so often at the very worst end of the spectrum. If you're dealing with—for some reason we really don't understand—what is effectively persistent pulmonary hypertension, but just beyond the newborn period, then that may be a very different scenario. And we don't always know how to distinguish idiopathic pulmonary hypertension and persistent pulmonary hypertension. In my experience, severe idiopathic pulmonary arterial hypertension presenting in the first few years of life is nasty, even though we do have long-term survivors. They are surviving on high doses of epoprostenol with or without other therapies and they still have appalling echos and ECGs and are receiving some of the strongest treatment regimens even though they are able to go to school.

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**Dr Abman:** Yes, there is as an important distinction here. Often people refer to persistent pulmonary hypertension as "primary" pulmonary hypertension of the newborn, when there is an absence of lung disease, but it's really a different disease. This transitional group, that is, the young infants who don't have classic persistent pulmonary hypertension features, is unique. Persistent pulmonary hypertension generally resolves over time with aggressive, early therapy and rarely leads to chronic pulmonary hypertension later in life. In striking contrast, some neonates or very young infants present with more striking pulmonary hypertension that is sustained beyond the typical treatment course for persistent pulmonary hypertension or is poorly responsive to therapy. In addition, some infants present later during infancy (after the first weeks of life), who have made the normal transition at birth, but are symptomatic during the first months of life. The question is, what to do with these infants, and what do they really have? These children form a unique subgroup of patients. As Dr Haworth and others have written, many of these children have structural lung abnormalities, often with variable degrees of alveolar simplification and lung hypoplasia. Again, these features make them quite different from simply being a smaller version of a patient with idiopathic pulmonary arterial hypertension.

## Idiopathic Pulmonary Arterial Hypertension

**Dr Haworth:** That's right. Idiopathic pulmonary arterial hypertension, whether or not you've got the abnormal gene, or whether or not you've identified it in your patient, is just what it says. So they have normal lung parenchyma, they have normally developed lungs and you can control them. And you can give them many years. But I've never seen one come off pretty intensive therapy even though they're at school and doing well. I think the other group you mention is very important. That is a pediatric group where the children have some evidence of pulmonary hypertension and perhaps chronic lung disease, they may have been premature, or they may just have had nasty infections in early life. Or they may have a degree of pulmonary hypoplasia and so forth. But there's a parenchymal element in this. The pulmonary hypertension may be unrecognized or its significance underplayed until the child is really very ill. That's a disease group I think we could, and should, help more than we do.

## Use of Nitric Oxide

**Dr Rosenzweig:** That's a good point. What are some of the current treatment strategies, and do you see them applying to patients in the neonatal period? Let's say, for example, with congenital diaphragmatic hernia patients? Or even bronchial pulmonary dysplasia patients in the future? There is not much supporting data.

**Dr Abman:** In premature babies, a couple of studies clearly demonstrate that pulmonary hypertension can contribute to their overall pathophysiology, especially in those with oligohydramnios or severe sepsis. But much pulmonary hypertension therapy, especially with inhaled nitric oxide, can have multiple effects, such as improvement in VQ mismatch, reduction in lung inflammation, or other properties, distinct from the effects on pulmonary vascular resistance alone, and what we target in some of the ongoing studies and what we use nitric oxide for in the premature infant can be quite diverse.

Many patients who are prematurely born with severe pulmonary hypertension have been shown to be quite responsive to inhaled nitric oxide, at least acutely, and patients can often come off nitric oxide with good resolution of their pulmonary hypertension. Others seem to have a more sustained course and are at high risk for developing bronchopulmonary dysplasia or chronic lung disease. Among our infants with severe bronchopulmonary dysplasia, we are seeing a strikingly high incidence of pulmonary hypertension. Our therapeutic approach is to first target their parenchymal lung disease in terms of looking for associated airway abnormalities, such as subglottic stenosis and cysts, bronchomalacia, tracheomalacia, and other lesions, and we try to optimize ventilator management to lower mechanical factors that influence pulmonary vascular resistance.

In addition, chronic aspiration can contribute to the severity of lung disease, leading to worsened pulmonary hypertension as well. When we find persistent echocardiographic evidence of pulmonary hypertension, we're pretty aggressive about performing cardiac catheterization in order to confirm the diagnosis and assess the severity of pulmonary hypertension, and to rule out associated abnormalities that may be contributing to it, such as left ventricular dysfunction or pulmonary vein stenosis. At least while they are still in the hospital, we often treat our patients

with chronic nitric oxide therapy. We are seeing a fair number of these babies, however, in whom nitric oxide therapy alone does not seem sufficient. So the question is what to add and what to do? Our nursery is much like many throughout the world, and we are often using sildenafil in the bronchopulmonary dysplasia population, initially in combination with nitric oxide, and we then gradually withdraw our patients from nitric oxide therapy for chronic oral treatment with sildenafil. I can't emphasize enough that in premature infants with bronchopulmonary dysplasia, pulmonary hypertension management really begins with optimizing treatment of the underlying lung disease and gas exchange, prior to the addition of pulmonary hypertensive medications.

**Dr Haworth:** I'm sure that's right. The problem in the past has been that a child is rapidly transferred form the care of the neonatologist or intensivist to a respiratory physician. And it is then that the pulmonary hypertension has been overlooked, unless the pulmonary hypertension was severe and self-evident early, while the child was still in hospital.

**Dr Abman:** Yes, and some of the babies who are going home with nasal cannula oxygen therapy may have extremely subtle findings of pulmonary hypertension on echocardiography.

**Dr Haworth:** Exactly. One can certainly imagine missing the diagnosis clinically when auscultating a chest full of crackles.

**Dr Abman:** Yes. When NICU grads are readmitted with their first viral pneumonitis, they can present with severe pulmonary hypertension. One of the major challenges in this population is to develop better noninvasive means of screening for pulmonary hypertension, deciding which patients need cardiac catheterization, and which infants are at high risk for pulmonary hypertension.

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**Dr Haworth:** With really good echocardiography you can get a long way nowadays, and it should be possible to pick up those children. Because even if you can't get an accurate assessment of the tricuspid jet velocity, you should be able to get a very good idea of right ventricular function.

**Dr Abman:** Right. Another contributing factor is that infants with bronchopulmonary dysplasia are a very reactive population, in whom even mild hypoxemia can often lead to striking vasoconstrictor responses. If these babies are discharged home with borderline oxygenation, or if they have elements of intermittent hypoxia due to sleep apnea—and with growing pressure to lower oxygen therapy because of issues about retinopathy of prematurity—chronic hypoxia can lead to late development or progression of pulmonary hypertension, for which we need to screen more effectively.

**Dr Haworth:** We've always recognized in the newborn that any increase in pulmonary arterial pressure is disproportionately great in relation to the degree of parenchymal change. We've always known that. And I think that's one aspect of what you're saying now. It's true.

## Indications for Lung Biopsy

**Dr Ivy:** What about the current indications for lung biopsy? We have done lung biopsies in children with interstitial lung disease or concern for alveolar capillary dysplasia, and occasionally for patients with a question of pulmonary venoocclusive disease. What is your thought on the current indications for lung biopsy in congenital heart disease? Are there other indications we should be considering?

**Dr Rosenzweig:** We rarely perform lung biopsies, except if we suspect the patient has another form of pulmonary vascular disease, for example, pulmonary capillary hemangiomatosis or pulmonary venoocclusive disease, which would not be amenable to targeted pulmonary hypertension therapy. Even then, I've treated a couple of patients with, let's say prostacyclin therapy, who appeared to have idiopathic pulmonary arterial hypertension and, at some later date, had a CT scan suggestive of one of these other conditions. Although you wouldn't expect the patient to respond, some secondary patients have had mild improvements with targeted pulmonary hypertension therapy. For that type of patient, I wouldn't necessarily perform a biopsy to confirm, if there is a high suspicion on high resolution CT. But those are the patients I would refer early for transplant, knowing they could rapidly progress.

**Dr Abman:** I agree. We generally recommend lung biopsy in cases where we find infiltrates or disease on chest x-rays or CT scans, especially with respiratory signs that we cannot explain. Generally, there must be something more than just pulmonary hypertension per se. We have some neonates who are near-term babies who require mechanical ventilation and have pulmonary hypertension with parenchymal disease. In these infants, we test for genetic abnormalities in surfactant protein or metabolism, including SPC, SPB, or ABCA3 abnormalities, or other disorders, such as pulmonary interstitial glycogenosis or lung hypoplasia. We've had some patients with pulmonary vascular disease that seems disproportionate to their lung disease. These are cases that need a more aggressive work-up, including earlier lung biopsy. There have been a couple of cases where venoocclusive disease or pulmonary vein stenosis has been apparent from the biopsy, and that's been helpful. But again, usually we reserve biopsy for cases where there is an undiagnosed parenchymal lung process.

**Dr Haworth:** If we break it down into the three groups of patients with pulmonary hypertension we see most commonly, there are the newborns, those with idiopathic pulmonary arterial hypertension, and those with congenital heart disease. In all

these conditions it is now very unusual to perform a biopsy. We will perform a biopsy in sick neonates who are ventilator-dependent when we suspect that pulmonary hypertension is not necessarily driving the whole picture and where we have good evidence of parenchymal lung disease but are not sure about its causation. Is it pulmonary hypoplasia, or pulmonary dysplasia, and is the disorder compatible with survival? Such children will undergo biopsy in order to determine their management. Are we ever going to be able to get this child off the ventilator? A biopsy is taken in order to find out whether more intensive medical management would enable the child to survive. So that is one very sad group.

We do not perform biopsies in children with idiopathic pulmonary arterial hypertension now, except in extremely unusual circumstances. In the group with congenital heart disease the only children who would have a biopsy are those with an elevated pulmonary vascular resistance in whom we think it just might be possible to do an intracardiac repair. Were a repair to be carried out, then the child would probably need prolonged, aggressive pulmonary hypertension therapy after the repair. It is possible to do this and, in the end, produce a child with normal pressures. But these children are the exceptions.

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**Dr Rosenzweig:** We don't often do biopsies in that group. But maybe we could open up one more question in terms of patients with congenital heart defects. How do we really determine operability and how do these patients differ from the straight idiopathic hypertension group in terms of treatment modalities? Are we certain that we can really apply these treatment modalities that are available to the congenital heart population yet?

**Dr Haworth:** Do you mean postoperatively or preoperatively?

**Dr Rosenzweig:** In either case. I think that's a good question. Should we pretreat patients who are borderline operable with targeted vasodilator therapy? Or do partial closure and treat them postoperatively? And which agents do you use? Is it still just epoprostenol? Or would you consider using something like sildenafil in the perioperative period?

**Dr Haworth:** If you're talking about pretreating in order to bring them into an operable range, we just don't have enough data. But it's a catch-22 situation because if you give something like, say, sildenafil and you're doing that in order to lower the pulmonary vascular resistance, you'll increase the shunt flow and damage the endothelium even more. So, it is almost a circular argument. I think we have become very good at managing the postoperative period. Very slick indeed. The issue then is what you do with a patient who had sustained postoperative pulmonary hypertension in the presence of what you hope is now an anatomically normal heart. That's much trickier. In my experience, many patients receiving maximal therapy, which includes epoprostenol and other drugs, do not do well. There's no doubt about it, they seem to get an accelerated form of pulmonary vascular obstructive disease if you don't get the timing of the surgery exactly right. And the other group, of course, is those in whom the timing of the surgery was appropriate, but they have never had a normal pulmonary vasculature. Their pulmonary vasculature never adapted normally to extrauterine life and they have always had a higher resistance than they should. So I think those with postoperative pulmonary hypertension are a mixed group. But they don't do well.

## Managing the Eisenmenger Patient

**Dr Rosenzweig:** Right. And, what about the straight Eisenmenger patient, whose condition you're not going to repair?

**Dr Haworth:** The classic Eisenmenger patient?

**Dr Rosenzweig:** Yes, a classic Eisenmenger patient, an older child. How do you approach that child differently than you would a patient with idiopathic pulmonary arterial hypertension? Is it still okay to just leave that patient alone? Or now that we have oral agents, although there's not a substantial amount of data, should we start to consider these patients for treatment as well?

**Dr Ivy:** It obviously depends on the age of the patient and how the patient's doing. If it's a teenager with a large ventricular septal defect who is doing well, who has no sign of right heart failure clinically or on echocardiography, who's quite active—the question I would have is, what is the goal of therapy? And as you said, for a classic Eisenmenger patient, I do not believe the goal of therapy is for an operative repair. The goal of therapy may be to improve quality of life. In a patient who is doing well, who has a 6-minute walk of 500 or 600 meters, with no sign of right heart failure, I guess in that patient I'm more hesitant to start an additional pulmonary hypertension therapy. However, in a patient who has limited exercise tolerance or some sign of right heart failure, I'm more likely to consider an oral therapy.

**Dr Haworth:** I think it's tricky, this one. I agree that one would have reservations about treating patients who are relatively well and have good exercise tolerance and that one would feel much more positive about treating those who are obviously symptomatic. I think there is a lot of confused thinking about the whole issue of the Eisenmenger syndrome. The aim of treating a patient with the Eisenmenger syndrome is to improve quality of life and longevity. Short trials, 12-week or 16-week trials, are not going to give you the answer to longevity, which will have to be judged against the natural history of the particular type of intracardiac abnormality. That sort of study will take years to complete and will be very valuable.

**Dr Rosenzweig:** I think that's a challenge.

**Dr Haworth:** Yes, it's a huge challenge. But if you're looking at how you can improve quality of life, then in a way it's much easier to do. The bosentan trial was promising, but it's very short term, and there is a sildenafil trial in progress. So we'll have some idea about the impact of these drugs on quality of life. But we are going to have to wait and see the outcome of much longer trials to assess any impact on longevity.

## Designing Future Pediatric Trials

**Dr Rosenzweig:** Let's shift gears a little bit in terms of the future of pediatric pulmonary hypertension and studies designed for children. We just mentioned one barrier specific to Eisenmenger patients. But we seem to face several barriers with children in designing long-term pediatric trials. Any thoughts about how we can improve on this in the future? Or how we're going to ultimately determine which agents are working best for the children?

**Dr Ivy:** If you look at the current problems or difficulties in enrolling children in some of the pediatric pulmonary hypertension trials, it is clear that not just a national effort, but an international effort is needed to get conclusive data. Most of the data we have currently are retrospective, and rarely, if ever, are randomized or placebo controlled trials performed. We're behind our adult colleagues in that regard. We have to stand together and say we need these types of trials to really know how to treat our patients.

**Dr Rosenzweig:** Pediatric registries will help that. But again, trial design is challenging in this group.

**Dr Haworth:** I think two factors are worth mentioning. Certainly national and international cooperation will get us there faster. But the other issue concerns trial design. It is no longer possible to do placebo-controlled trials in idiopathic pulmonary arterial hypertension. This is a nasty disease and the median survival is 10 months in untreated, classic idiopathic disease in children. It's unethical to do placebo controlled trials. That would also be true for the adult population. You've just got to treat if the diagnosis has been confirmed. The reason industry doesn't really like to talk about trials in Eisenmenger patients is that studies in this patient group entail very long-term trials for anything meaningful to come out of them. Industry has been very recalcitrant when it comes to pediatric trials in general, but both the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products (EMEA) now require pediatric study or trial data, actual or proposed, to be submitted when requesting a drug be licensed for adult use. From that point of view, the outlook is much more optimistic and positive than it was a few years ago.

**Dr Abman:** What's unique in pediatric pulmonary hypertension, outside of different features of idiopathic disease and patients with Eisenmanger syndrome, is the neonatal population and infants with bronchopulmonary dysplasia, lung hypoplasia, congenital diaphragmatic hernia, and other developmental abnormalities of the lung. There hasn't been a concerted effort to explore the impact of pulmonary hypertension in those populations and how to best approach it in them. This is a wide open area, and we can really benefit from multicenter studies. The other thing that's unique from those patients is that their pulmonary hypertension is so tightly linked with pulmonary vascular growth and lung growth, or alveolarization. So there are clearly unique issues in the young infant with pulmonary hypertension, which as pediatricians, we need to approach more aggressively.

**Dr Haworth:** That's right. In congenital diaphragmatic hernia the association between lung growth, alveolar development, and peripheral arterial development is very well recognized. One of the practical problems is the wide spectrum of the disease, the degree of lung hypoplasia. This wide spectrum makes it quite difficult to perform trials of any drug or treatment regimen in these patients. It is a similar problem in chronic lung disease, isn't it? The degree of parenchymal involvement and so forth is so variable. It's hard.

**Dr Abman:** Some clinician-investigators are trying to apply infant lung mechanics and perhaps measurements of diffusion capacity in infants, but this remains experimental.

## Calcium Channel Blockers and Sildenafil

**Dr Ivy:** I would like to ask another question. Is the use of calcium channel blockers in young children who are reactive and under one year of age a good therapeutic option? I have not been as impressed with the response in these children, and they seem to have more side effects than older patients.

**Dr Haworth:** I don't know. If you get a nasty case of idiopathic pulmonary arterial hypertension and in the first year, you are very lucky to get a positive responder. I have not had one. Whether one could give nifedipine rather than sildenafil to infants and young children with moderate pulmonary arterial hypertension and say, chronic lung disease, congenital diaphragmatic hernia, and those sorts of things, we don't know.

**Dr Abman:** Now it seems there's a shift, for example, in the bronchopulmonary dysplasia population. An early study demonstrated acute responsiveness to calcium channel blockers, but the study was performed while infants were hypoxemic, and the response was not greater than with increased oxygen alone. There are also concerns regarding potential negative side effects of calcium channel blockers in these infants.

**Dr Haworth:** Probably right.

**Dr Abman:** So again, we share the feeling that other agents, such as sildenafil, may be a better choice in infants with bronchopulmonary dysplasia, but data are lacking in this group. We remain concerned with potential toxicities, such as retinal disease, especially in young premature infants. Perhaps we have become too comfortable with sildenafil in infants at too early a

stage, before knowing enough about the potential for toxicity. So far, we have not seen adverse events in our patient population, but our concerns persist and we urge caution.

**Dr Haworth:** I agree. You might be interested in a child I have been treating recently. She had been treated with sildenafil and is a strange child, rather like a Russell-Silver dwarf, but not proven to be so, and she had done well with sildenafil. I recatheterized her the other day because I did not want her taking sildenafil indefinitely. The pulmonary vascular resistance came down to a very respectable low level with nitric oxide and her treatment has been transitioned to nifedipine.

**Dr Ivy:** Is she under a year old? Or one to two years?

**Dr Haworth:** No, she's a tiny little thing of about three.

**Dr Ivy:** Okay.

**Dr Haworth:** And the reason for wishing to give her nifedipine rather than sildenafil is that we have considerable long-term experience over many years with nifedipine. It doesn't seem to have done anything terrible to anyone. And sildenafil is an incredibly potent drug with which we have very little long-term experience. If we have to use it because there is no alternative, then that is acceptable, but if there is an alternative, I feel I should use the alternative drug.

**Dr Rosenzweig:** On a last note, have you seen patients whom you've treated with sildenafil become acutely responsive? I've seen a couple who were nonreactive before and at least moderately reactive with sildenafil therapy.

**Dr Haworth:** And what was the etiology?

**Dr Rosenzweig:** Idiopathic patients. But it's just a curious finding.

**Dr Haworth:** I do not treat de novo patients who have idiopathic pulmonary arterial hypertension with sildenafil as a monotherapy. All the children who have been referred to me on sildenafil, who have been on sildenafil for some time, have died as soon as they have arrived in the hospital. It has been awful and I think one of the dangers of the oral drugs is that people just give them the tablet and only when the patient is obviously deteriorating rapidly do they transfer them to a specialist center. Sildenafil may be much safer and more effective in the older patient, as the recent trial would suggest.

**Dr Rosenzweig:** I want to thank everybody for your opinions and expertise. This has been an extremely valuable discussion. ■