Approaching Pulmonary Hypertension - Pediatric Grand Rounds-20261016_073003-Meeting Recording

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Calderon, Delia started transcription



Calderon, Delia 0:07

Ready to go.



Sutter, Deena E 0:09

Okay, good morning, everyone. Welcome to Pediatric Grand Rounds and happy Friday. Before we start, Dr. Mustafa has a reminder for you, so I'm going to turn it over to her briefly.



Mustafa, Shamimunisa B 0:22

Hi, good morning everybody. Just a quick reminder and thank you, Dina, for allowing me to do this. On the standpoint survey, please, please can you take out some time to complete this? The e-mail was sent on October 6th and if you
have accidentally deleted it in your haste to delete all those extraneous emails, please go ahead and e-mail the Standpoint server and they'll send you a personalized e-mail as well. And as of Wednesday, we have a, the Department of Pediatrics has a 16% response rate. So hopefully
This time next week, it will be wonderful if we can get it, if we can double it. Thank you so much.



Sutter, Deena E 1:09

All right, thank you so much. Everybody, just please remember to go ahead and fill out your survey. I know I will do that now that you've personally reminded me. So today we have the honor of having Dr. Megan Griffiths to do our Grand Rounds. She's an assistant professor of Pediatrics at UT Southwestern Medical Center.
and Director of the Pediatric Pulmonary Hypertension, Director of Pediatric Pulmonary Hypertension in the Division of Pediatric Cardiology. She received her medical degree from the University of Colorado School of Medicine and completed

pediatrics residency at the University of Connecticut and Connecticut Children's Medical Center, where she served as chief resident.

Leigh Shapleigh 1:29
Director of pediatric pulmonary hypertension, director of pediatric pulmonary hypertension in the division of pediatric cardiology.
She received her medical degree from the University of Colorado School of Medicine.



Sutter, Deena E 1:48
She completed pediatric cardiology fellowship at Johns Hopkins as a pediatric scientist development program fellow, followed by an advanced fellowship in pulmonary hypertension at Columbia University Irving Medical Center. She is now board certified in pediatric cardiology. Her research uses proteomic proteomic and metabolomic approaches to identify, understand, and treat pulmonary vascular disease and right heart failure in children. She is a principal investigator in the Pediatric Pulmonary Hypertension Network and led development of the pediatric individualized risk score. So everybody, thank you for being here and welcome to Dr. Griffiths. I'll turn it over to her.

Megan Griffiths 2:33
Thank you so much for having me. Let me go ahead and share my screen.
And if someone can just confirm for me real quick that you can see everything.

jeannine kaufmann 2:45
Yeah.



Calderon, Delia 2:46
Tess.

Megan Griffiths 2:47
Okay, perfect. Well, yeah, thank you so much for having me. I love talking about pulmonary hypertension, so I'm very excited to be here. So today I want to talk overall about an approach to pulmonary hypertension or how I think about this systematically. Just some quick disclosures, I'm supported by Children's Health, but I also have some grant funding funded by Janssen. I've been a consultant

for Merck and majority of the drugs that I'm going to talk about are off-label. Pretty much every pediatric PH Med and PD is off-label.
But I want to talk to people about what's the definition of pH, what is normal, and let's talk about the multiple causes of pH and start thinking through a more systematic approach to identify and treat this. I'm going to go through a bunch of specific cases and give you a lot of specific details, but what I really want you to take away from that
from all of this is that pH presents in these many different ways with these many different causes and subtypes. And the first thing we have to do is understand the subtype and all the treatment comes pretty easily after that. Please feel free to ask any questions and I'll have my contact information at the end if anyone wants further questions.
And for any of our fellows or residents in the audience who think you might be interested in pediatric cardiology or pulmonology and want to do PH, it's a great field and there's lots of space. So please join.
So some cases, these are people who have presented to my office or the archetypes of people who have multiple times presented to my office. With a 13 year old, previously healthy, she was seen by her pediatrician for chest pain. She's got sent to cardiology and is found to have very severe pH by echo.
If A five-month-old, this baby was a 24-week infant with 600 gram birth weight, had a PDA closure, had neck, now stuck on CPAP, stuck on oxygen, and you just can't wean this baby. You have a three-year-old with a hypoplastic left heart who's had a Norwood Sano and Glen who's now needing oxygen and nitric.
We have a one day old who was born full term at birth, has respiratory distress and hypoxia, is now intubated on nitric oxide for PPHN and needing increasing amounts of vasopressor support.
So all of these patients have pulmonary hypertension. They will meet the hemodynamic definition of pulmonary hypertension. But each one has a distinct type that needs to be treated differently.
So if we think globally about what this is, it's actually a diagnosis made by cardiac cath. So give your good friendly cath Dr. Dr. Heibel, a call anytime you're wondering about this and she can help you out. But this is defined nowadays as a mean pulmonary artery pressure by cath of at least 20 millimeters mercury.
So in this picture here, you've got a heart and you have a Swann catheter floating in through the SVC, through the tricuspid valve, out the pulmonary valve, and it's sitting

here in the pulmonary artery. And Dr. Heibel is measuring your pressure. And if it's over 20, you've hit the definition of pulmonary hypertension. Now for pulmonary arterial hypertension,
aka pulmonary hypertension that's happening on the pre-capillary side. That has an additional definition, which requires a wedge pressure, aka the left side of the heart to be low pressure, so less than 15, and something called the pulmonary vascular resistance index, the PVR, to be greater than three. And if you're seeing that, call your friendly cardiologist and they can help you interpret those hemodynamics.
But the key, that is a key point to remember because pulmonary arterial hypertension is what we're treating with drugs.
Can people ask, because this definition used to be 25, and we lowered it to 20, and I get a lot of colleagues who say, well, you guys just changed the definition. And now it's 20, you just have more patience, but it's really a meaningless definition. And that's not quite true. Where that actually came from was this great paper by Brad Marron in 2016,
where they looked at on a population level more than 60,000 cardiac caths. And granted, this is adults because it's a large population study, but it gets the point across. And when you're looking at such a large study, they were able to see that most people, the majority of people's mean pulmonary artery pressure is here around 10 to 13 millimeters mercury.
So if for the average one of us, myself, or those in the audience, if we were to go get a cardiac cath, our mean pulmonary artery pressure is like 10 to 13 millimeters mercury plus or minus 3. What they found is that when people hit 19 and above, this is their hazard ratio of mortality, their hazard ratio of mortality starts going up.
at every 1 millimeter mercury above 20. And they did the same thing with that pulmonary vascular resistance. So based on that, that's how we have our new definition where we say 20 and up is our threshold.
When we think about this in kids, kids get complicated because we have all these different developmental ages and stages. And of course, we as pediatricians know that we're dealing with congenital diseases, developmental diseases, cardiac diseases in partial stages of repair, babies in the NICU with respiratory failure.
kids with metabolic diseases. And what we find in kids is that this is from the Pediatric Pulmonary Hypertension Network, which is a national group here in the US. It's about 50-50, about 50, 45, 50 percent of these kids fall under that group one category, so pre-capillary.

A lot of those are due to are due to congenital heart disease. And the other 50% are chronic lung or some kind of lung disease. And in Pediatrics, the majority of that is developmental lung disease of prematurity.
Now, this disease causes about one in 500 hospitalizations, at least I think it might be more nowadays. But these patients have a three-fold higher mortality compared to any other pediatric ICU patient. And they can have a five-year mortality of anywhere between 25 and 40%, depending on the etiology.
So how do I see this when somebody calls me and they say, I need a pulmonary hypertension consult? I go take a look at the patient and I go through a couple things in my head. Do they have abnormal pulmonary vasculature? Do they have abnormal lung parenchyma? Is there some kind of abnormal blood flow or anatomic abnormality? So
What kind of pH am I dealing with? Did this happen just a moment ago or is this a long-standing chronic process? How's the right ventricle doing? And what's their risk? Because that's how we determine treatment in this disease. So
The other way that I ask this to myself is, okay, the blood is supposed to come. It's supposed to get through the SVC and the IVC and get to the right ventricle. Now my right ventricle is at high pressure. Where is the blood stuck?
Is it stuck at the pulmonary valve? Then I'm calling a cardiologist. Is it stuck at the branch of pulmonary arteries? The patient has tetralogy. Again, I'm calling a cardiologist. Is it the pre-capillary microvascular bed? That's probably me. Is it the post-capillary microvascular bed? Is it the pulmonary veins? Is there something wrong with the left side of the heart?
Is there something wrong with something like the aortic valve or is the left ventricle not functioning and they need to call heart failure?
Then my next question becomes, okay, I know where it's stuck. Why is it stuck?
And that's where I think about how does this actually work in infants and children. And it's really a multiple of many, many things. We know we have this in a normal kid. We have this nice, thin-walled, flexible, responsive pulmonary vasculature. In the setting and a lot of kids of
injury, whether that's abnormal blood flow, hypercarbia and hypoxia, inflammation, infection, lung immaturity, we end up getting this very, very thick-walled hypertrophied pulmonary artery. And that over time leads to RV hypertension, and RV failure.
So let's filter this down into guidelines. The World Symposium on Pulmonary

Hypertension had their last meeting in 2024. And this is kind of the schema that the pediatric group came up with. They divided this into two sides. So your patient with pH, they either are somebody without cardiopulmonary conditions.
Those are usually IPAH, or in peds, and this is what I'm going to spend more time on, patients with cardiopulmonary conditions. So let's think about, let's start thinking through some of these cardiopulmonary conditions, because remember, this is the majority of our patients. So we have here, remember, CHD, congenital heart disease, and developmental lung disorders.
Let's start in the neonatal period. This is where a lot of our pulmonary hypertension hangs out with all of our NICU colleagues. Kind of think about this in a few different groups. We have that congenital heart disease group, the developmental lung disorders group, the ones with a large shunt, like a PDA or a BSD or a lot of AVMs. and then some patients with some post-capillary disease, so left-sided disease.
We're going to evaluate these a few different ways. In the Nicu, I always start with a targeted echo. And at my hospital, we now have a nice pH echo protocol that includes some key measures that I'll show in a minute. I often do a cardiac CT. It gets me all the vessels and the heart, but it also gets me high-res pictures of the lungs. And then I consider calling my friendly local cath doctor.
Other things that I always look at, if I'm trying to see that hyperkinetic with high flow, or if I think the right ventricle is dilated, maybe there's extra blood flow, I might go and look at the abdomen and see is there a shunt there, or I might get cardiac MRI with flows, or I might consider if there is a shunt to try and get rid of it. If there's congenital heart disease,
Start calling a cardiologist and maybe a PH cardiologist. That one gets a little bit complicated and is probably out of the scope of a one-hour talk.
But once I think about that, I go back to my same schema. Does this patient have abnormal vasculature? Do they have abnormal lung parenchyma? Is the blood flow abnormal?
So here's a baby who came to me not too long ago. This baby was an ex-preemie, now about 5 kilograms and has a VSD. And here, this is an apical 4 chamber of their heart.
Here it is with blood flow and that hole right there, that's the VSD.
So what do we do with this baby? This baby is still in the Nicu. This baby can't get off positive pressure. This baby has a VSD. And now anytime the baby cries or poops, this baby is desaturating. So we went to the cath lab and we have systemic

pulmonary artery pressures. So mean PA pressure is 46. We're above 20. We've hit that definition for pulmonary hypertension.
severe. It's the same as the systemic blood pressure. So this is bad pulmonary hypertension. That pulmonary vascular resistance is high. It's above 3. So we've had the definition for precapillary pulmonary hypertension. But there's also a lot of blood flow to the lungs. So this is a big shunt. These lungs are getting pounded with extra flow.
When I give this baby nitric oxide, there is 2 1/2 times as much blood flow to this baby's lungs as to the body. So what do I do? I now have developmental lung disease, pre-capillary pH, and a big shunt.
This is always when I run back to what does it look like here? So I have pH associated with CHD, and I potentially have a correctable shunt. So I want to go for my evaluation for operability.
and consider, can I treat this? Can I close this shunt?
And if we go and look, there's your cardiologists, I think, know this one pretty well. How do we evaluate operability? So patients who are good candidates, PVR less than four, sorry, that's not this patient. But lots of pulmonary blood flow, that tends to make you a good candidate. This patient sits here in this borderline range.
where their PVR is high, they definitely have pH, but also this shunt is beating up on those lungs. So we want to get to close this if we can. So this is a patient who I'd probably call something like a treat and repair. So I'm going to put them on pH meds and time it with my surgery to get them treated.
Let's go back to the NICU. So that patient went off to surgery. We're going back to NICU rounds and going to see our next one. Developmental lung disorders. This is 50% of pediatric PH, and this is a difficult group. They are complex, they are small, they are difficult to treat.
Our neonatologists are working tirelessly to both prevent developmental lung disorders and then to treat them when they come up.
But these are the patients who when I look at them, I say, okay, you're maybe not primary abnormal pulmonary vasculature, you have abnormal lung parenchyma. And with that, you may be developing abnormal pulmonary vasculature. And what's really interesting here is that the alveoli, when we're thinking about a preemie baby, the alveoli and the vasculature are going to grow together. And then we have to think, did this just happen or has it been happening over time?
So let's go back to our embryology. We're pediatricians. I love embryology. And if we

think about the growth of the lungs, we start with the lung buds and we end up with alveoli. But these acinar testacular stage, acinar tubules testacular stage, that's around the 24 week mark.
So at this stage, we're really just getting some alveoli. They're not real alveoli. They're very, very immature. And we're not even really at a proper capillary bed.
So the babies that are born in this extreme prematurity age.
They have very limited lung cross-sectional area, but they also have very limited pulmonary vascular cross-sectional area. These babies don't tend to do so well with pulmonary vasodilators. We can give them all we want, but the stuff, the parenchyma and the vessels just aren't there.
And then I always remind people, 36 weeks, 36 weeks, which is pretty much the last week of prematurity, is the first week that you have a fully developed pulmonary vascular bed and the first week that you have an actual alveoli. And if you're a full-term healthy baby with no problems, you are born with about
30 million alveoli. By the time you're a couple years of age, you have 500 million. So those first couple years of growth is a massive increase in pulmonary surface area and pulmonary vascular surface area. And that's our superpower here as pediatricians is we get to use growth.
So if we go back to our fetal circulation, remember in fetal circulation, the babies aren't using their lungs and they don't need pulmonary blood flow. So in fetal circulation, we have a foramen ovale. Blood goes right to left across the foramen ovale and fills the left ventricle. And blood going out the pulmonary artery goes right to left across the ductus arteriosus and provides the body.
Less than 10% of blood actually goes to the lungs in fetal life.
At the time of birth, you take your first breath, the lungs suddenly open, and that pulmonary vascular resistance plummets. And if we take a look at what's happening in the first part when a baby first takes their breath, it's not so much of a drop of pressure. It's a massive increase in pulmonary blood flow.
So this is in the 1st 5 minutes, and you can see the mean PA pressure at birth is about 60. And after about 30 minutes, that mean PA pressure is still 50. But they went from barely any pulmonary blood flow here in the red to tons of pulmonary blood flow. So what happens if that transition doesn't occur? That's what we call PPHN.
persistent pulmonary hypertension of the newborn. This is different. This is that transitional phase. So if I were to go think about this in my way, I'm thinking, okay,

we've got something abnormal with the vasculature, maybe something wrong with the lungs. This is the acute one though.
And in this case, that PVR didn't drop and we didn't get enough blood flow. If we don't have enough blood flow, we have severe hypoxemia and circulatory collapse. These babies, I tend to just focus on saying, okay, what was the underlying cause? Was there HIE and recooled? Is there meconium aspiration? Is this a DTGA and they're really hypoxic and they
also just had cardiac surgery and they're just a little bit too stressed out and inflamed and things aren't transitioning. And our job then is to just support the heart and support the right heart through this until whatever the inciting cause goes away. Sometimes it doesn't go away. We've all seen those PPHNs, I think, where they come in, they are blue, they seem normal, like they're full term, they're not dysmorphic, they don't have meconium, they're not septic, but something is just not right and they're blue. And that's when I send genetics. This was a genetic study of PPHN, of what we call idiopathic PPHN done by
Barry Nogi's group at Johns Hopkins, and they found that 44% at that time had an identifiable gene. Quite a few of these, unfortunately, were not actually or were very unlikely to survive out of the neonatal period. The big one I'll point out here is alveolar capillary dysplasia with misalignment of the pulmonary veins. I've seen a couple already this year.
The gene mutation is called FoxF1. For a full FoxF1 deletion, they're very unlikely to survive past the neonatal period.
Let's go back to the bigger developmental lung disease, the one that I think we all struggle with, bronchopulmonary dysplasia. So chronic lung disease of prematurity, that baby born less than 28 weeks, who has that very, very severe alveolar phenotype, where their lungs just aren't growing, they're difficult to ventilate.
They have these heterogeneous areas where they've got scarring and over compliant lungs all mixed together. And they're sitting in the NICU on the ventilator, or they're sitting in the NICU on positive pressure and we just can't move them forward. And then they develop pulmonary hypertension. What's going on here? What's really going on when they start developing pulmonary hypertension with this is that they aren't growing enough lung.
If they're not growing lung, they're also not growing pulmonary vasculature. And after a while, that's going to show up on the echo. And so the treatment for this is ultimately to grow the lung. So here's this baby. This is a patient with severe

bronchopulmonary dysplasia who also had severe pulmonary hypertension, and we ended up going to the cath lab.
And these babies get so complicated because they can be so multifactorial. And I'm going to go into a couple of the things, but use this baby as an example. When I went to the cath lab for this baby, this baby was premature. This baby has severe developmental lung disease. And here's my cath diagram here on the left. This is what's called a Mullins diagram.
Your friendly cath doc will make one of these after they go to the cath lab. And you can track all of the pressures and saturations. So blood came in, went out to the lungs, came back, and they sampled the blood in the pulmonary veins. The saturation in this baby's pulmonary veins are 84 to 87%.
So despite being on oxygen, this baby's pulmonary veins are desaturated, suggesting this baby's lungs are not moving oxygen.
The next piece is this baby's mean pH pressure right here is 27. We're above 20. We've met the definition for pre-capillary pH. That 27 doesn't seem that high, but the systemic mean pressure is 45. So this is more than half systemic. This is actually pretty severe.
And then when I go and take a look at the pressures in the left heart, I've got some pressures here that are actually quite high. So this baby also has high filling pressures. What that means is blood that goes out to the lungs is at high pressure and it's struggling to get back to the left heart.
and that's what I call post-capillary pH. So this baby has three different types of pH all happening together.
So how do we treat this? These EPPVDN, that's the European Pediatric Pulmonary Vascular Disease Network, has a really, really nice flow chart, this one, for assessment and treatment of PH and BPD. And they always start with your screening echocardiogram.
with targeted measures, which I'm going to go into. And then you optimize ventilation. And after you've optimized ventilation, go and repeat. And in this case, your goal is to get all of the lungs together. I tend to have a pretty tight PCO2 goal because my goal is not to over ventilate the kid. My goal, if possible, especially if this baby is term corrected,
So I want to see all of the lungs recruited, growing, and starting to participate in gas exchange. Only after we've done that do I start thinking about actual pH mints.
So this is my reminder for everyone treating BPDPH. I'm going to get a t-shirt with

this written down one day, but no alveoli left behind.
So how do we take care of these? I'm going to give a brief slide about chronic phase ventilation for BPD, but really this is not just a one slide thing. This is like a five-hour talk. So I'm going to leave that to my pulmonology and NICU colleagues who know this much better than me. But this very heterogeneous lung disease
when you saw that chest x-ray that had all of this kind of...
almost reticular look, what we have is areas of lung collapse and areas that are over-distended. And we want to try and recruit all of the lung evenly. So we use this very large tidal volume given at a slow rate, and our goal is to fill the lung completely. and give enough time for the air to go from the more compliant over-descended areas into the under-ventilated areas next to them. And then since so much of these babies have an obstructive phenotype, we want to give them a slow rate and let them exhale. And this particular paper is from a group at CHOP who are looking at what they call
essentially the lost effort, wasted effort, and they use very high PEEPs to overcome this. In this study, you can see some of these PEEPs are astronomically high and they actually are able to improve exhalation with some of these high PEEPs. Typically, I'm not advising ever on any of these kind of super high PEEP strategies. I go to our BPD pulmonologists for that because that starts to get
a little out of my wheelhouse as a cardiologist.
But I think the most important thing for pulmonary hypertension and bronchopulmonary dysplasia is the multidisciplinary approach. So this study came out of the group at Seattle, the Stanford group has also shown this as well, where once you start developing pH in BPD, it's a sign that your BPD is much, much worse and that pH is associated with very
high morbidity and mortality. Some reports are up to 30%. And the thing that seems to make the most difference is having a coordinated multidisciplinary effort. And I can tell you for my practice up at Children's Health in Dallas, about two years ago, we started forming our multidisciplinary BPD team with a discrete group
of neonatologists, pulmonologists, the PH team, so that we're all doing things similarly. We're all seeing the babies all together as a group on a, we meet now twice a week, and it's really, really improved our outcomes, especially our ability to ventilate and take care of these very, very sick severe babies.
Pharmacotherapy for this, sildenafil is probably the number one thing you're going to see. And there's quite a good bit of evidence. These are all studies showing

sildenafil in the BPD population. And what we know from this is that pulmonary vasodilators are safe and effective.
When we start them in this population, they do reduce pulmonary artery pressure and they improve RV function. However, none of them have ever shown to have a true long-term benefit and they do not alter your lung disease course. All they do is support the right ventricle for a period of time while you're working on the lungs. So that's why I always go back to this.
And I start with optimizing ventilation.
The other side of this, remember we were talking about this baby who has pre-capillary pH. Okay, so maybe we're putting them on some sildenafil. They are very poorly ventilated and they're not moving oxygen. So pulmonology and NICU are going to work together and improve their ventilation.
But this baby's filling pressures are also high. This is what I call left ventricular diastolic dysfunction. This is getting increasingly recognized, I think, in the neonatal period. And my colleague Kara Goss, who's an adult doctor, who's an adult PH Dr. is actually looking at this long-term.
And one of the number one findings we find for these babies over time is that they have left ventricular diastolic dysfunction. So in the adults, we would call that heart failure preserved ejection fraction. And this is persisting both in the neonatal and infant period and can persist to adulthood. We don't know why. Is this steroids? Is this PDA exposure? Is this an immature myocardium that didn't grow
because of prematurity, is this catechol effect? We don't know the answer. What I do work on nowadays is having a normal blood pressure. When I see bad cases of this, I go straight to milrinone and start limiting the nitric. And I've honestly started using sometimes some heart failure management.
But this paper from the Colorado group, you can see this baby here with severe BPD with that very reticular appearance was poorly oxygenated. They started nitric oxide and these lungs just totally fluffed out. And that's characteristic diastolic dysfunction. This baby has pulmonary hypertension.
but the problem is truly in the left ventricle. And when I give them the pulmonary vasodilators and I'm working on the right ventricle side, I actually cause injury. So something to certainly keep an eye out.
So we've talked a little bit about some abnormal blood flow and abnormal lung parenchyma. Let's talk about abnormal pulmonary vasculature and RV failure. So RV failure is the most important thing in all of pediatric and adult PH. We always talk

about, or you'll always hear about, oh, this is the pulmonary artery pressure or the TR gradient was this. It was half systemic.
It was two-thirds systemic. It was less than half systemic. It was super systemic. There is no mean pulmonary artery pressure that predicts outcomes in pH. It is all RV function. And the thing that I always go to is what we call RVPA coupling. RV, right ventricle to pulmonary artery coupling. What that means is that
at a given pressure, the right ventricle is able to tolerate that pressure. And if the pressure goes up, the RV can increase its ability to contract and match that. So for example, I'm sitting here right now. My mean pulmonary artery pressure is a certain amount. My right ventricle is pumping.
If I get up and go run around the block, my RV can get it together and pump the blood that I need to go run around the block. In a baby whose RV who has pH and has uncoupled RV or PARV uncoupling, that means maybe they're sitting there right now and they are okay. You have them sedated, they're in the ICU, they are okay. But if the pressure goes up, if their demands go up even a little bit, that RV is going to fall apart. So maybe that means the baby poops and falls apart. The baby has a tantrum and falls apart. The baby sedation gets a little bit off and falls apart. The baby has surgery or sepsis, and suddenly the pH has decompensated.
And how does that look? Well, let's just go to what the RV should actually look like. So if we have a normal ventricle, the left ventricle is round, it's thick walled, it's very muscular and strong. And the RV is kind of thin.
It's smaller, it's thinner, it's not as efficient. I always call it the big spoon. It's, you know, kind of hangs along with it, with the LV. And what happens is this RV is like a bellows. That interventricular septum is a stable wall for the RV to contract against. When you have pH and that RV wall starts pushing into the LV.
you lose that stable place to contract. And you end up with a heart that looks like this. So this tiny squish thing here in the bottom, that's the left ventricle. And this giant not moving bag of fluid, that's the right ventricle. And if that LV wall, if that interseptal, that septal wall is pushed over into the LV,
you no longer have that bellows to push against like this. Instead, the ventricle is just kind of rocking back and forth. And that gives you very, very inefficient contraction and that child is going to go into heart failure.
So some examples. This one's normal. Here's a nice round LV. Here's a skinny little, I'm the big spoon, I'm the lover, skinny, doing its job, RV. This patient has systemic pH, but the RV pressure is the same as the LV pressure. But look, the septum is right

here in the middle.
and this RV isn't super dilated and it's holding on. This one, this little sliver here, this is your LV and this bag of fluid that's not moving, that's your RV. Here you've lost RVPA coupling and this patient is in heart failure.
There's lots of good ways to assess this by echo. And I recommend having a nice targeted echo protocol. This is some of the measures on that European Pulmonary Vascular Disease Network. And I'm going to go through a couple of my favorites.
So if anyone has read echo reports, for example, for the Nicu babies, you've probably heard of, you've probably heard the term septal flattening or septal flattening in systole probability of pH. I like to quantify that. So this is called the eccentricity index. Take a picture by echo.
Remember that LV is supposed to be round, and I can do the two dimensions of the LV. If it's truly round and I divide them together, it's one, normal eccentricity index. If that septum starts flattening, that dimension 2 starts lengthening out. And when I divide dimension 2 by dimension one,
you get a high number. Above 1.3 is kind of where we're starting to think pH. If I'm starting to see eccentricity indexes above 2, I get pretty worried. But this is a nice way to quantify septal flattening.
In those same pictures, your friendly cardiologist can also measure the diameter of the RV compared to the LV and do it in a ratio. This is from Penny Jones' group at Children's Colorado, and they looked at this RV-LV ratio. Remember that RV is supposed to be small? Once that RV starts getting bigger than the LV,
that patient has a very bad outcome. So here we have an RV-LV ratio of 0.5. These patients are doing okay. Once this RV-LV ratio is 2, you can see here the purple on this curve, those patients have a very poor outcome.
And one of my last things I love to do is what's called free wall strain. And this is a better measure or a consistent quantitative measure of RV function. So your cardiologists puts this thing called strain tracking when they do the echo and more negative is better. And if we look at its long term,
These patients who had less negative strain, so more positive strain, so that's bad actually. More negative, better, more positive, worse. So these patients who had worse strain did much worse. Patients who had pretty good numbers, they did well.
And this patient here, she had a PDA open. She never went above systemic pressures. Here you can see her free wall strain is minus 22%.
Put her over here on this curve. She's doing pretty well.

So brief recap, because we're about halfway. We talked about the definition of pH. We talked about some of the types of pH, pre-capillary, post-capillary, lung disease, and thinking through, let's figure out which one to determine what type of pH we have.

Let's think about treatment. Let's talk about drugs, everyone's favorite. So I'm going to go back to that first case. This 13-year-old healthy female came in with chest pain to a cardiologist and has severe pH. She's also got multiple episodes of syncope, and that syncope is happening with exertion, and she's got increasing shortness of breath.

So this is called an apical 4 chamber. This is the right atrium, the left atrium, right ventricle, left ventricle. Remember I said the left ventricle is supposed to be rounder and bigger than the right ventricle? So you can see pretty clearly here, this RV is huge. This LV is squashed. This is her short axis.

This little sliver that's being squished, that's her left ventricle. This big thing, that's her right ventricle. So this is bad pH.

So what are we going to do?

Well, my first question, what does she have? I went through and did some studies on my echo and a CT. She doesn't have abnormal blood flow. I looked at her lungs. She's never had a pulmonary history. She wasn't premature. She has no reason to have lung disease, but I will do PFTs, checked abnormal lung parenchyma.

This patient has abnormal pulmonary vasculature.

And she looks like she's in RV failure. So we should figure out what's her risk. What's her risk for things going badly?

And that is how we determine treatment in group 1 pH. And my big message here, which may be a little different to what people are used to, is to get aggressive. So we're going to risk assess and say, is this patient lower risk or higher risk? But notice here that every option is some kind of combination therapy.

What drugs are approved for kids? It's not very much. So I said I was going to use off-label stuff. I sure am. Only sildenafil and Bosentin have been FDA approved for kids. And something called Celexapag was just approved in May of this year.

And how do we assess risk? Well, the adults have really good ways. They have all of these risk criteria or they have this reveal score, but they don't really apply to kids that much. You'll see. I'll show you here in a minute. Some of their major criteria are things like age over 60, applies to zero of our patients.

But what happens when we do a risk-based treatment? This study is from the French

group, and this is adults, but it's still a great study. They took a bunch of their patients who showed up and they divided them by risk. So here's their highest risk group. So the most read, they're the worst patients. And they saw what did we treat them with? Did we treat them with single therapy, dual therapy, or triple therapy? And these worst patients who showed up on triple therapy at one year or at first follow-up, they were doing the best. They had improved the most, and not just because they had more space to improve. They objectively met more low-risk criteria. And when we looked at their survival,

Here's in the red, here's these higher risk patients who got put on triple upfront therapy. The green and the blue, this is a survival curve, death or transplant, and we're looking at 10 years. At 10 years, 90% of these worst possible patients are still alive, whereas only 50% of those combo patients are still alive. So

I show this to my patients when they come in and say, hey, let's get really, really aggressive because I want your child to be in this 90% over here.

And when they propensity matched it, they found the same thing.

So that's why lower risk now goes combination therapy, but higher risk goes to triple combination therapy. Let's just briefly talk about the lower risk. None of my patients, if they are in that true pre-capillary pH group, none of my patients are just getting sildenafil anymore. Everybody gets a minimum combo therapy.

That came from this 2015 ambition trial where they looked at patients getting tadalafil, ambrizentin, or combination. And it's been redone in something called the ADU trial where they looked at equivalent types of drugs. And what they found is that when we did combination therapy,

50%, we had a 50% reduction in mortality. And on every curve, so here is ambroxentin monotherapy here, combination therapy at the top. Here's tadalafil monotherapy, combination therapy at the top. When you put them together in every possible way, combination therapy worked

better. So based on this, we now just recommend combo therapy up front. This just was recently looked at in Pediatrics, came out I think last month in the European Respiratory Journal. This is 500 pediatric patients, I think about 2003 to 2021. And these are patients who are either put on single therapy and then escalated to combo therapy

were put on combo therapy and then escalated to triple. And every single time, the patients who were on the higher, more aggressive combo therapy up front did better.

But this requires us to assess their risk, and how do we do that? So...
Problem with adult risk measures is they require things like running on a treadmill or age over 60. And remember I said so many of our patients are in the NICU and I can't get my NICU babies to do a six minute walk test yet, so I'm trying. So we've been working really hard on coming up with an actual pediatric group.
With the PPH Nets, the Dutch National Network, and a group called ReHIPID, which is Spain and Latin America, we've been working on putting together a comprehensive risk score so that we can figure out what's your likelihood to have a bad outcome within one year. And we actually just recently released this, and it does work well, I can tell you.
validated across multiple countries. And our goal long term is to have a nice little online applet where you can enter in your patient's data, or even better, have it added into Epic so that it can just pop into your notes and tell you, hey, this patient is at moderate risk, or this patient is at high risk. They need aggressive therapy.
The other big thing is, let's say we did dual therapy. What about triple therapy?
And what if that triple therapy, I said, a prostacyclin doesn't work. There's a nice new drug on the market. It came about two years ago, so keep an eye out for this. And this is the first drug that's actually hitting vascular signaling. So when I think about pulmonary hypertension, I think about what's actually going on at a molecular level.
And this is super exciting. You're going to hopefully see this soon. I know the adults are using it a lot. I'm using it a lot.
what's actually going on in this disease. I said abnormal vasculature. So we have this whole TGF beta pathway that none of us truly understand. But right in the center of that, we have two sides. We have the BMP side that is a little bit more anti-fibrotic, anti-angiogenic, and we have what's called an active inside.
that's a bit more pro-angiogenic. So we have a very careful balance in all of our blood vessels between growth and growth regulation. And what we think happens in pH is that anti-angiogenic, anti-growth side gets down-regulated. And so we have a misbalance.
that active inside that is now hyperactive and is pro-proliferative and causing all of this abnormal growth of these vessels. There is now a drug called Zetadercept that binds up these activins and the goal is to bring everything back into balance.
This was released in 2020. This was the 2022 cellar trial. And you can see here in these adults, the patients who got put on cetadercept here on the top of the survival curve did way better than the patients on placebo.

And the survival difference is, you know, 5.5% events in the cetadercept group, 26% events in the placebo group. So FDA approved this for adults. This is fully enrolled in a pediatric trial called Moonbeam, and I believe the results will be out in 2028. But we did just publish our pediatric experience on cetadercept, and this is across the US pediatric pulmonary
retention network. This is about 65 patients. And what we found was when we put our PAH patients on this drug, this is them initially. So initially, about 50% of these patients were in functional class three and four. Those are patients who can't walk. Those are patients who are fainting. Those are patients who are high risk for an adverse outcome.
And after cetadercept, 90% of them are in functional class one and two. So functional class one is no symptoms and functional class 2 is minimal symptoms.
We found that the patients who were able to do a six minute walk test, which is how far can you go in 6 minutes, pretty much all got better. And I can tell you one of my patients who was enrolled in this study was non-ambulatory before this and is now able to walk with some assistance. She was just, she's got some other issues, but essentially
Her cardiopulmonary function was so limited prior to this, prior to this drug. She's now actually walking.
And when we looked at hemodynamics, a good portion of the patients, their mean pulmonary artery pressures went down, their PVRs went down, and their cardiac function remained the same. So this drug does seem to be effective in this population as well for the group 1 pre-capillary PH group.
Now, it does come with a lot of side effects. There's a non-trivial risk of major bleeding, that means brain or hemoptysis, as well as some other potential vascular side effects. But it's our first truly disease modifying agent in pH.
So we talked about our patient, this patient with abnormal pulmonary vasculature. We ruled out abnormal blood flow. We ruled out abnormal lung parenchyma. We said this is chronic. She has an RV failure. We risk assessed her, probably say she's high risk. And then we determined treatment. In her case, I actually put that patient on quadruple therapy. So she's on
with a great outcome. So my take home points here, what I want everyone to learn from this is that pH is multifactorial. We have that hemodynamic definition, but soon as you get to that hemodynamic definition, your next question needs to be, why does the patient have this? Because that's going to determine your treatment.

We can have pre-capillary disease, left-sided heart disease, can be reactive, can be autoimmune, it can be lung disease. But you have to treat the underlying cause or the pH doesn't get better.
Multimodal therapy for that group 1 pH is key. And especially for that idiopathic group, that's probably time to pull in an expert. And there's now three centers in Texas that all have pH specialization. And then no matter what kind of pH it is, support that right ventricle. Assess the risk.
see how bad is this right ventricle and support that right ventricle. Even if you're trying to fix some other underlying thing, you got to support that right ventricle until you fix it. This is some members of my team. Stacey over here on the left is my nurse. Jillian is my pharmacist who makes everything happen.
And this is how you can contact, this is my online hashtag and you can contact me as well at megan.griffiths at utsouthwestern.edu, which I believe is on the sheets that they sent out. And check us out online. Our hashtags are the people's ventricle and no alveoli left behind.
And with that, I'm going to take questions.



Sutter, Deena E 49:04
Thank you so much. That was a great way to explain this to people who do not understand the physiology, which is me. I always tell the residents, I'm not smart enough to be a cardiologist. So I really, really appreciated that. So we have questions in the chat.
If anybody wants to put in a question or...
Let me see if I can see anybody's added anything here.
or people can raise their hands if they have a question.
So really quick, just for the general pediatricians out there, you know, you talked about patients who are presenting in an older age that were unknown to have any underlying disease. Are there any clues? I mean, in general, obviously, if kids are syncopal without a good explanation, that kind of thing, but you did describe

MG

Megan Griffiths 49:52
Mhm.



Sutter, Deena E 50:01
the one patient who came in at 13. Are there any are there any clues here that are

really going to strongly suggest that this is what the severe pulmonary hypertension that was not previously recognized, you know, former preemie should trigger them to, you know, reach out. I mean, obviously getting an echo for any underlying cardiac disease is important, but any thoughts on that one?

Megan Griffiths 50:22

Mhm.

So I think risk factors, I've definitely had, I had a couple patients who presented that were kind of missed. And then when you dug into the history, you found out they were former preemies. So that's a huge risk factor. Any kind of family history? I think that it's one of those where it's really just looking at what are my cardiac red flags because pulmonary hypertension is one of the sudden cardiac death.

kind of red flag ones, you know, up there with hypertrophic cardiomyopathy that we're really going to make out our determination based on echo. That patient, she was having syncope and she ended up in cardiology first on accident, but they were actually leaning towards neurology. But the things that I start asking are,

It's shortness of breath with exercise is going to be your first presentation. Because as you have to augment your cardiac output to do any exercise, that's when they're going to see symptoms. So the kid who just doesn't want to exercise, who gets short of breath, say walking down the hallway, and I start getting pretty specific about my questions and I say, okay, where

Going to the grocery store. Parking. This is the regular Kroger Tom Thumb. We're not going to Costco or Walmart. Regular grocery store. Are you short of breath between the car and the front door? Can you make it through the vegetable aisle? And some of these kids are short of breath with that. Or math class to English class in your middle school.

are you short of breath with that distance? And some of them, it's shocking. They really are. And that patient who I described, she was short of breath between the mailbox and a house when she was trick or treating with her siblings.

Sutter, Deena E 52:10

Okay, yeah, that sounds pretty severe.

Megan Griffiths 52:13

Yeah, I mean, she was severe, but when you really went back into her history for

maybe a year or two, flight of stairs, one flight of stairs, and she was catching her breath. People always blamed it on obesity for her. And they were like, well, she just needs to lose some weight. She needs to work on her diets. But one flight of stairs, That shouldn't make you short of breath. The other hints are, let's say they've gone to high altitude, are the symptoms worse? So she was always visiting family at high altitude in Mexico and she had severe symptoms and I had to tell her, sorry, you can't go visit your family right now.



Sutter, Deena E 52:33
Yeah.

MG **Megan Griffiths** 52:48
which was pretty rough for them. I canceled Christmas.



Sutter, Deena E 52:54
Well, I really appreciate you presenting today. And everybody, if your CME credit is available, the code is in the chat, so please claim your CME. And thank you again, Dr. Griffiths, for that great presentation. We really welcomed all of your wisdom. Thank you so much.

MG **Megan Griffiths** 53:11
Thank you.

Calderon, Delia stopped transcription