Bench to Bedside: Research Focused on Improving BPD Outcomes

Each year 13,000 to 15,000 extremely premature infants develop severe bronchopulmonary dysplasia (BPD). Despite major advances in neonatal intensive care and improved survival of infants born very prematurely BPD rates have not decreased over the last decade. While there are several reasons for this, a lack of understanding of the various paths to this disease, and the absence of personalized therapies have contributed to this problem.

Researchers at the Donald Thibeault Lung and Immunology laboratories are focusing their efforts on understanding how bacterial blood stream infections injures the developing lung and cause BPD in premature infants. Recently, Venkatesh Sampath, MBBS, MRCPCh, a physician-scientist with Neonatology at Children's Mercy hospital was awarded a five-year grant by the National Heart Lung Blood Institute (NHLBI) to study the role of inflammatory angiogenesis in the developing lung. The major goal of this project is to understand how pulmonary endothelial immune activation during sepsis promotes lung inflammation and alters the formation of lung blood vessels predisposing to BPD. In collaboration with other researchers in the laboratory, center for infant pulmonary disorders, and clinicians in the NICU we hope to develop strategies and new therapies to decrease the burden of BPD.

Hear from Venkatesh Sampath, MBBS, MRCPCh on what their ongoing research tells us about how babies develop BPD and the other studies that are underway to investigate and treat BPD at CMH and Neonatology.

Featured Speaker:

Venkatesh Sampath, MBBS

Venkatesh Sampath, MBBS, MRCPCh is a scientist and neonatologist at Children's Mercy Kansas City. Dr. Sampath completed his residency in pediatrics at Royal College of Physicians and Child Health Affiliated Hospitals, United Kingdom in 1998 and at Cleveland Clinic Foundation in 2003. D. Sampath completed his fellowship in Neonatal Perinatal Medicine at Royal Australian College of Physicians Affiliated Hospitals Australia in 2001 as well as at Cincinnati Children's Hospital in 2006. Having had no prior research exposure Dr. Sampath was fascinated by the pulmonary biology research being conducted within Neonatology at Cincinnati. In the last decade, Dr. Sampath has been probing at the how and the why behind premature infants developing life-threatening diseases such bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC). At Children's Mercy we are developing a comprehensive research program to understand how bacterial-mediated lung vascular injury alters vascular development and contributes to chronic lung disease in premature infants.

Learn more about Venkatesh Sampath, MBBS (http://www.childrensmercy.org/findadoctor/details/14711)

Transcription:

Dr. Michael Smith (Host): So, our topic today is "Bench to Bedside: Research Focused on Improving BPD Outcomes." My guest is Dr. Venkatesh Sampath. He is a scientist and neonatologist at Children's Mercy Kansas City. Dr. Sampath, welcome to the show.

Dr. Venkatesh Sampath (Guest): Oh, welcome. Thank you.

Dr. Mike: So, what have we learned so far about the "how" and the "why" behind premature infants developing BPD?

Dr. Sampath: Right. So, I think the last 20-25 years, we have learned a lot of new information. In the ‘90s, early in the ‘90s when there were tiny babies who were surviving and getting BPD, the traditional thought was that a lot of oxygen use and being on the mechanical ventilators, the artificial breathing machines, was the two most important causes of premature babies getting lung disease. To a large extent, we've been able to mitigate those factors. They are still players, now, but with the way we artificially ventilate these babies is much more gentler and how much oxygen we give to these babies is treated very closely. So, with those measures, we've been able to . . . We saw a decrease in BPD rates in the ‘80s and ‘90s. Subsequently, in the last 15 years, we have not been able to make much progress and that is because, I think, the survival of the tiny babies has improved, so more babies are at risk of developing lung disease. And the other factors, the one that I'm particularly interested in, is understanding how lung inflammation is caused infections directly in the lung, or infections in the blood stream, cause BPD. I think that since BPD is a very complex disease and multiple factors are involved in causing the disease, the things that we can decrease, factors like increased oxygen use and artificial ventilation, those are things with which we have made a lot of progress, but there are other areas, other risk factors that have cropped up in the last 15-20 years which we are addressing, but they seem to also have become very important players for causing the disease and also particularly because a lot of the small babies are surviving, and because now we have new survivors, a lot of them are at risk of lung disease. So, I think what we have learned in ‘80s and ‘90s is that oxygen toxicity and artificial ventilation can injure the lung and to some extent, we have made a lot of progress on that. More recently, by which I mean that 15-20 years, what we are beginning to understand is that infections that are directly in the lung, or in the blood, can affect lung disease pretty badly; could cause lung disease badly. And also, genetics also plays a major role. So, I think the focus, right now in the last 15, 20 years has been going towards infections and the genetics basis of lung disease. So, I think we have learned a lot and, to a large extent we have mitigated some of the risk factors, but since BPD is a very complex disease, we are learning new information which needs to be dealt with to decrease the rates of BPD further.

Dr. Mike: Right. Well, let's talk about the infections that you mentioned. So, exactly what has been the theory or the hypothesis of how these bacterial infections are affecting the developing lung and vasculature in premature infants?

Dr. Sampath: Right. So, that's one of my pet peeves because what I noticed, when I was in training as a fellow in Cincinnati, and immediately after and I became faculty, is I would see these babies who would not be ventilated too long, and would not have too much oxygen for too long, but they would get you know, just one or two infection episodes, and then they would get this disease. So, obviously, we found…I was really interested in dissecting the role of infection in lung disease. And so, what we think currently, is that when our babies get infection in the blood stream, and because they're premature,

they have an unregulated immune system. So, what happens when they get an infection is that though you treat them with antibiotics, the infection and the body's response to infection creates a huge inflammation in the lung. And, in adults, this is seen acute lung injury or ARDS. So, we see a similar picture in some preterm babies who get infections and because of that acute inflammation in the lung, what happens is that the lung is injured and rather than lung . . . during this inflammation process, a lot of proteins are secreted that digest the lung, in fact, and also cause injury to different cell types, increasing endothelial cells or the [inaudible 05:29] cells. Those also can result in BPD. You know, my specific focus has always been on the lung endothelial cells and the reason we are very interested in those cells is that how does an infection in the bloodstream cause inflammation in the lung? What's the connection? And, I think one important connection there is the lung and endothelial cells, because the endothelial cells senses this inflammation and the lung endothelial cells secrete a lot of molecules which attract the inflammatory cells into the lung. So, they inadvertently, in trying to fight the infection, the lung endothelial cells are also pulling these inflammatory cells into the lung tissue and that sets up this whole inflammatory cascade to contributes to BPD. The other important part of that same story is that the lung endothelial cells, when they become inflamed, behave differently. Normally, they do the usual thing. They grow, they maintain the integrity of the lung vasculature, but when they get inflamed, they do other things and they affect how new blood vessels are formed. So, when lung blood vessels, lung endothelial get inflamed, they have a propensity to form abnormal blood vessels and we know in babies who die with BPD, the vasculature is very abnormal. So, my interest in studying how these endothelial cells get inflamed and how that endothelial inflammation contributes to inflammation in the lung, but also contributes to abnormal vascular formation which is seen in babies with BPD. So, that's really my focus.

Dr. Mike: So, this is fascinating, right? So, you've found that there's this connection between the infection, the dysregulated immune system in the premature infant, and there's a release of cytokines, these inflammatory compounds; there's a direct insult onto the endothelial lining itself, but at the same time, that's causing an abnormal angiogenesis in the lungs.

Dr. Sampeth: Yes. Yes.

Dr. Mike: So, you've made this nice connection all the way…So, where are you at in all this research, now? You've put together this wonderful hypothesis and this pretty linear connection. Where are you at in all that?

Dr. Sampath: Yeah, I'm glad you asked this question, because we're really excited. Our lab-I have to thank my lab members for doing this great work, but the first step was actually showing that this sort of . . . a lot clinicians knew this kind of thing existed, but we wanted to prove in a mouse model that this existed. Typically, if you look at animal models of lung disease, you know, we need animal models to study lung disease. And they have used oxygen toxicity or ventilation in rodents or bigger animals, in sheep, for example, or lambs, to cause lung injury. So, we first wanted to ask a simple question, if my hypothesis is correct, can I create BPD, or something similar to that in the mouse without using the typical risk factors, which is the oxygen toxicity or the ventilation toxicity? So, we just published a paper in you know, American Journal of Respiratory Cell Biology. We showed in the neonatal top, if you give one dose of LPS in the peritoneal space, which mimics the sepsis, or infection, one dose or two doses, just that, no oxygen toxicity, nothing else, that alters lung development with less vessels and less alveoli. So, that is a proof of concept paper.

Dr. Mike: We know that the LPS, too, just to bring it back for a second, the LPS is really strongly pro-inflammatory, right? So, that's making your connection between going back to that original thought that the infection and the inflammatory response is really what's underlying all of this abnormal angiogenesis down the line, right? So, that is your proof of concept, correct?

Dr. Sampath: That is my proof of concept, because LPS, as you correctly pointed out, is drawn from granulating to bacteria and granulating to bacteria are among the worst pathogens in babies. A lot of babies that get that die, but a lot of survivors get bad lung disease. So, we took a component of that LPS, which is drawn from granulating bacteria, showing that in proof, the LPS from bacteria can, in the setting of developing animal, in the setting of the developing lung can injure it in such a way that you get abnormal development, abnormal blood vessels, causing BPD. So, that was, I think, the first, because we want to first prove that our hypothesis is correct and we can develop a mouse model to prove it. So, subsequent to that, then now, I think what we are doing is we are playing it in two different ways. We are trying to understand, what are the normal mechanisms which keeps endothelial cells intact and how those mechanisms are altered. So, an important clue that we are finding out and we are excited about it and we are hoping that in 2017 we publish a key paper on this, is that it looks like when the lung grows, like every other organ, you need angiogenesis for normal lung growth itself. So, there's some master regulators of lung growth called Delta-like 4, it's just a gene--it's a very critical gene that regulates lung growth, and what we are finding is that LPS can alter Delta-like 4 sigmoid. So, we now have come to a second line of proof, which can we show a relationship between inflammation and endothelial inflammation and bacterial sepsis, and how angiogenesis mechanisms, which control how blood vessels develop are altered and we haven't published yet so I don't want to make too much of it, but, you know, our data is very strong and I'm hoping that we'll come out in 2017 that we can show there are very critical angiogenic mechanisms which are altered that LPS or bacterial products.

Dr. Mike: Well, obviously, so, Dr. Sampath, when you make that connection, right, and you prove your hypothesis here, because now, when I step back and I look at this starting with the bacteria ending with the abnormal angiogenesis, what you're laying out are many potential targets for treatment now early on. And, of course, because that's really what this show was about, was how were we going to improve outcomes in BPD and so you've laid out a nice theory of how this all develops and I already see it in my mind. You know you have these potential areas that you can target to treat and really make the outcomes improve for these infants. This must be obviously a very exciting time for you right now.

Dr. Sampath: Right. It's a very exciting time and I must say that one simple way we can do this, even before we try new therapies, which everybody does now, is that we…if we decrease infections, bloodstream infections, that's going to have an effect itself, but despite our best intentions, you know, some of these babies are going to get infected, so if you understand the molecules which are involved in this, let's say in this pathway which causes abnormal blood vessels, then there are molecules. For example, angioprotein 2 is a key molecule in the middle. And so, we have target antibodies against that which can potentially decrease this whole cascade and prevent BPD. Or, at least decrease the instance of BPD.

Dr. Mike: So, lots of biologic agents, yes.

Dr. Sampath: Yes.

Dr. Mike: Yes, that's great. So, I just want the listeners to also know, Dr. Sampath, that you were awarded a five-year grant by the National Heart, Lung, Blood Institute to study the role of inflammatory angiogenesis in the developing lung. So, I just want the audience to know that and, listen, this is fascinating work, it was great having you on the show, and I want to say good luck to the rest of your research. So, thanks for coming on the show. You're listening to Transformational Pediatrics with Children's Mercy Kansas City. For more information, you go to www.childrensmercy.org. That's www.childrensmercy.org. I'm Dr. Mike Smith. Thanks for listening.