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Updates in Pediatric ECMO: Challenges and Opportunities

In this episode of the World Shared Practice Forum Podcast, Dr. Dennis Daniel discusses pediatric extracorporeal life support (ECLS) with experts Drs. Peta Alexander and Ryan Barbaro. They explore the differences between pediatric and adult extracorporeal cardiopulmonary resuscitation (ECPR), highlighting differing causes of cardiac arrest and the interpretation of recently published studies. The discussion also covers supply chain issues affecting ECMO availability, the importance of standardized, evidence-based practices to identifying ECMO-associated complications, and opportunities for future research into ECMO use and outcomes.

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Voiceover *00:04*
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Dennis Daniel *00:18*
Welcome to the World Shared Practice Forum Podcast series on OPENPediatrics. I'm Dr. Dennis Daniel, ECMO Medical Director in the Medical Surgical ICU at Boston Children's Hospital and Associate Director of OPENPediatrics. We're very pleased today to welcome two luminaries in the fields of pediatric extracorporeal life support, Dr. Peta Alexander and Dr. Ryan Barbaro. Dr. Alexander is a Senior Associate cardiologist and director of the ECMO program at Boston Children's Hospital and Associate Professor of Pediatrics at Harvard Medical School.

Peta Alexander *00:45*
Great to be here. Thanks.

Daniel *00:46*
Dr. Barbaro is Service Chief of Pediatric Critical Care Medicine and Director of Pediatric ECMO at CS Mott Children's Hospital and Clinical Associate Professor of Pediatrics at the University of Michigan.

Ryan Barbaro *00:57*
Thanks so much. Great to be here.

Daniel *00:59*
Peta, Ryan, welcome. All right, let's get right into it. Let's talk about pediatric ECPR, which is a topic of, I think, great interest around the world. And in particular, there's been a number of recent publications in the last couple of years exploring ECPR in and out of hospital, cardiac arrests, adult, pediatric. Most of the prospective work in this area has been in the adult ECMO population. Ryan, could you help us start, just to orient, you know, how is the pediatric ECPR population different from adults who are receiving ECPR?

Barbaro *01:30*
Yeah, I think you know, one of the places where we see a lot of the focus of the research right now, especially is in out of hospital, cardiac arrest, and thinking about if ECPR can serve a role in helping to resuscitate those adult patients who don't recover in typical fashion after cardiopulmonary resuscitation and defibrillation. However, those patients are almost always had a primary cardiac event, often an arrhythmia, sometimes a heart attack. And those patients are then presenting to an emergency department, often receiving care on the way, being prepped for potentially an ECPR event where they'll be cannulated peripherally through the groin. Whereas our children who are being considered are most often patients who are within our hospital system, many of them would be in Dr. Alexander's unit or other units similar around the country after having received congenital heart surgery and have had a sternotomy in an open area where potentially cannulation can be the case. But I think where some of the difficulty in kind of marrying those two things is when we start to think about, could we potentially take the lessons that we've learned in those adult patients and extend them to out of hospital cardiac arrest in our pediatric population. And for a variety of reasons, those similarities just aren't there enough to make it transportable as we might like. And so, for example, our children often are suffering a cardiac arrest because of something more respiratory in orientation, something that you know, whether it's an illness, whether it was unfortunately a drowning or suffocation event, those patients were deprived oxygen and often are then suffer a cardiac arrest subsequently, and that situation is just a much different recovery than those patients who had a primary arrhythmia and may have ongoing lung disease. The other aspect is more technical in nature, and that many of the children who at rest are are smaller, both in terms of their vessels and in their body size in general. And so accessing those, those growing vessels during a cardiac arrest can be quite difficult. And if there's not a primary ongoing heart problem that's driving that arrest. Once oxygenation is restored, the heart kind of responds and is able to continue to perfuse, then what we might see in those situations is actually that that groin cannulation, pumping against a working heart can also create other problems in terms of delivering oxygen to the brain, because there's competing circulations with the ejecting heart If there's an ongoing lung disease component in that situation, then unfortunately, we're sending deprived oxygen to the brain and then that circulated oxygen through the ECMO circuit to the body. But it would come back and say, the primary distinction in my mind is really around the difference between the fact that our adults are often suffering a primary cardiac event in the out of hospital, circumstances that lead that arrest, and our children are often suffering a primary respiratory event. And then there are some technical differences in the cannulation.

Alexander *04:27*
And that's certainly referenced in the prospective observational studies of resuscitation in pediatric populations as well. There's been quite a lot more information that's come out of CHOP recently, and certainly referenced in the AHA guidelines for cardiopulmonary resuscitation. The cardiac population in centers that are established as ECPR centers. ECPR is recommended as a potential option for cardiac patients with cardiac onset disease leading to cardiopulmonary resuscitation, but not such a strong recommendation, or no real recommendation for ECPR in the non cardiac population. And so I think none of the studies that that that we're seeing come through in the adult population are likely to really change that the recommendations that exist for pediatric care at this stage, in my opinion.

Daniel *05:22*
So there's two kind of facets in this like adult to pediatric comparison. One has to do with differences in the technical factors in the circumstances that lead to cardiac arrest, and then the other has to do with

just the pediatric specific settings in which ECPR is sort of already present. Do you think that these adult findings in any way create more urgency or pressure in terms of developing the pediatric ECPR capacity. Or do you think it's so apples and oranges that the research has to come from the pediatric population to drive that?

Barbaro *06:07*
I would say on the pediatric side, that's probably the lesson that we should continue to try and articulate is, what are the circumstances and the situations outside of maybe that post cardiotomy patient with a recent sternotomy, where we think ECPR may have a role and may be able to be explored. I think an example of where I think folks have done a really nice job of thinking carefully around this is in the bone marrow transplant space. Even with that small population and this really specialized life support technology, people have been careful and thoughtful about using the relevant evidence within children to think about how we can define where we think this might be helpful and where it's less likely to be helpful. And I think that's a space where we could certainly work for it in the ECPR.

Alexander *06:50*
One of the things that I was thinking, not dissimilarly, is that the fact that the adult clinical care construct, the whole system, could get together to do interventional studies in this out of hospital arrest, cardiac arrest population, it kind of puts us back on the hook as a pediatric care provider group to think about how we can better get evidence generation moving for the pediatric population. We kind of let ourselves off the hook by saying it's really hard. Everybody does things differently. The patient populations heterogeneous, and yet, actually, with enough infrastructure and force of will, I'm sure, knowing the groups involved, they were able to move forward with these interventional clinical studies in a really difficult population to study, and so I think that really does lay down the challenge to us in the pediatric critical care space and the pediatric ECMO care provision space, to do better in terms of getting high quality evidence generated for the care that we're providing for children.

Daniel *08:01*
A call to action.

Alexander *08:03*
Call to action, indeed. The time is now.

Daniel *08:07*
I want to pivot to one major area of challenge in the last few years for pediatric ECMO, which is the supply chain. As you both know as ECMO directors, there's been significant supply constraints, limiting access to critical components, cannulae in the case of VV-ECMO, membranes, which obviously creates complexity in just providing ECMO, but also challenges efforts to standardize ECMO to understand complications and outcomes. Peta, what would you say is the current state of the ECMO supply chain for pediatric patients?

Alexander *08:44*
Wow, what a great question. And I know that you've got an international audience for the OPENPediatrics forum, and so I'm confident that there are different current statuses around the world. As we're experiencing it here in North America, in big centers we have access to all of the equipment that we need to be able to deliver ECMO care. But having said that, you know that we've had to change

our equipment over the course of the last 12 months due to shortages and unexpected recalls. And when the pediatric oxygenators the lungs from Getinge were affected, we had to scramble to work out how to support patients that would normally be supported on pediatric devices with more adult sized devices. And that required changes to the circuits for the ECMO support that we were using. And one of the things that came out of that, that Ryan and I both are acutely aware of, is that we were not able to give each other as ECMO centers good advice about how to temporize adult equipment for pediatric patients. And the more we dug into that, the more we talked to other centers, the more we recognize how different the care that we deliver at the bedside really is. And Dennis, you are and I are in the same institution, and you have the benefit of working across both of our units that provide ECMO. And so you know that even in our center, the ECMO care that's delivered in one building and the other looks very different, and the care processes are actually managed very differently. And so although we'd already started moving towards things like PEACE, the Pediatric ECMO Anticoagulation Collaborative and some other kind of consensus definitions around adverse events, the supply chain issues really highlighted again to us that pediatric ECMO care has evolved differently in every different program because the technology wasn't developed at the point where we were applying it to patients. And everybody did it differently. It's probably a good time now to start to bring groups together to talk about how we can get care delivered in a much more standardized way. And that's part of the backbone of some of the work that we've been doing over the course of the last few years with the anti coagulation collaborative, and then with the ECMO central adverse events, that start to just set a foundation for talking about things with a common language, talking about this care with a common language.

Barbaro *11:28*
For sure, one of the things that we notice in the pediatric space, I think, is that often we're constrained to use a smaller set of devices to occupy the same work as happens in larger size patients. That kind of adaptation and that consolidation of options, I do think, make us really vulnerable to disruptions and reliant on kind of talking to one another about how we can adapt in the space. We're really good at that. And you know, one of the things that some have challenged about is that maybe we're too good for our own good, which is just that, as we continue to adapt and make this stuff work, that actually we potentially depress the need to durably solve these problems. And so sometimes I think those adaptations, that flexibility and really innovation that we consistently demonstrate in terms of making things work is good, but also comes with some cost.

Daniel *12:27*
I was going to ask about exactly that tension, which is, you know, ECMO as a field, I think, is grounded in this principle of being solution oriented and willing to adapt. At what point does the advocacy then have to turn from making it work at the bedside to achieving a certain standard or a certain consistency that requires input? Not just from the centers implementing ECMO, but also from all of the stakeholders that facilitate that, including the manufacturers.

Alexander *12:57*
Yes, all of the different innovations at the bedside aside, we do believe that there is the potential to start to get some standardization of care and simplification of the care strategies for patient populations that may actually be to their benefit. One of the things that we haven't said out loud during this discussion is that if you look at the adverse events suffered by children who receive ECMO, they're still occurring at a vastly higher rate than in adults who receive ECMO care in a much more standardized fashion, because the point where adult ECMO really came to the fore, the technology itself was better

developed and actually better optimized for adult flows and adult dimensions, and because there's more patients at every given size who receive ECMO as adults, the the options and the market share and the potential to make a profit for companies who are involved in producing the equipment is higher for the adult population, and that's one of the reasons why the pediatric market and the pediatric device supply chain is so precarious. Its that actually we are dependent on a small number of manufacturers who are making a smaller number of products for a smaller population, for essentially a smaller profit margin for this group. The FDA is actually aware of this, and the FDA CDRH, the Center for Devices and Radiological Health, particularly the orphan diseases group, are really invested in trying to help find a path to reducing the barriers to pediatric device development and bringing new pediatric devices to market, and they've looked at some really innovative programs, including funding think tanks for breaking down some of those barriers, as well as building out infrastructure to be able to bring together groups of pediatric hospitals that would invest in bringing together data to inform the safety and efficacy of devices in general, including ECMO devices. And to help reduce the duration of testing those devices, getting enough evidence to achieve that safety and efficacy determination, and then to move them to market through reimbursement strategies. And so the FDA is working on this, together with investigators, trialists and industry sponsors. And we know that industry is aware of the pediatric population and the difficulties with supply chain.

Barbaro *15:41*
I think, you know, one other just tangible thing that we saw really impact practice at the bedside within this space was the loss of the dual lumen VV cannula for those smaller sized children. And then we could see, we could observe within the ELSO registry, that across centers, the rate of carotid artery cannulations, or VA ECMO through the neck increased substantially, and it was because of the loss of this cannula. And then a few years later, another cannula came onto the market, another dual lumen cannula, and you could see those, those carotid artery cannulations, move back, not actually all the way back to where they were before, though, but moving back. And so, you know, I think, to the extent that placing a cannula in the carotid artery, as opposed to just in the large venous return makes a difference to patients, then that's something that probably is impactful to kids in a real way, not just in a hey, we have to work around the system, and there might be problems that we're not able to articulate. In this case, we know that kids lost their carotid artery, or at least had a cannula placed into it because of the loss of this device.

Daniel *16:55*
Another important area of focus you've both mentioned relates to understanding ECMO associated complications and outcomes. You've both been instrumental in releasing ECMO Central, the adverse event definitions published in Lancet Child and Adolescent Health this past October. Peta, can you give us a look behind the curtain? What did it take to execute this effort? As far as I can count, 13 different professional medical societies endorsed this. How did, how did this come together? How did, how did the process go?

Alexander *17:25*
So in the way that so many really productive collaborations come together. This was a genuinely happy accident that came at the at the right point for a group of invested collaborators to really take the ball and run with it. So Ryan and I were both actually working with the FDA for different reasons. And it was actually one of the FDA program managers who suggested that we needed to get involved with a different process that was ongoing, and that ended up being published as the ACTION-ARC, which is

the Academic Research Consortium adverse events for pediatric VADs. So the pediatric VAD community had decided that they needed to move this forward because the adult VAD community had recently undertaken this process. And the Academic Research Consortium is a group who have some co leadership with the device section of the FDA, and they actually have been building out common adverse event for device trials in the adult cardiac space for 20 years. So they've got a huge background of being successful in this space. And the FDA so depends on them that when the adult VAD community had undertaken these adverse event definitions, they expected that the pediatric VAD community would take them on board as their adverse event definitions. And so the ACTION Network said, well, we've got a totally different population, and the adult VAD definitions are not relevant to our population. And so it was recommended that they undertook this process and that they looped Ryan and I in because they'd worked with us before as the ECMO team, so that we could add ECMO to the pediatric VAD adverse event definitions and just do all the mechanical circulatory support. But obviously the patients who are in a position to receive a primary VAD and those who receive ECMO as their primary resuscitative therapy are different populations, and so very quickly, it was recognized that we needed two separate but harmonized processes to cover both populations. And so even before we had our very first meeting of the leadership group to move forward the ECMO adverse event definitions that became ECMO-CENTRAL, we had a number of negotiations with the invested parties to make sure that we're on board with moving together two different processes with genuine preemptive harmonization. Ryan, maybe you can speak a little bit to the actual process we undertook from there.

Barbaro *20:07*
This opportunity of kind of defining adverse events gave us a cool opportunity to really work with folks from around the world, whether those be folks that were running clinical trials and needed to define adverse events within the ECMO space for those clinical trials in the adult and pediatric communities, or whether those were folks that were stakeholders at the bedside, patients and families, as well as our ECMO specialists, our physician clinicians, our nurses, as well as a number of folks that carried over expertise from device development as well as from regulatory bodies locally and internationally. And it was just, it was wonderful to really hear different people's perspectives on, you know, what was, what had worked, what hadn't worked, what was important, and to see people get excited about, I think, what can sound like a relatively mundane thing in terms of pediatric ECMO adverse events, but but people were engaged, and it was, it was a lot of fun. We were really wanted to make sure that whatever came of this, that it was potentially useful and meaningful, and we recognized that that meant incorporating the voices of folks that were stakeholders at a more professional level, whether that be professional clinical bodies or our research organizations. And so we were able to engage with a number of those professional societies from the beginning and allow them to help us to refine and improve on the process. And as a result, when we, when we reach the kind of the final definitions of these processes, they were willing to come along with us and endorse that work as named on the byline of the publication itself. And so that was, that was took, took some fun organization, a lot of great conversations, but definitely made for a better product.

Daniel *21:56*
Well, speaking from the other end of the process of now having ECMO-CENTRAL available and using it, I think, and you know, Peta can speak to this too, I think it's already sort of raised the bar of our quality improvement and just monitoring of ECMO, as well as the conversations we're able to have about ECMO from a shared framework.

Alexander *22:18*
I don't even know that I've told Ryan that we're actually adjudicating all of our adverse events as a clinical quality and safety ECMO committee for our M&M's according to the ECMO central adverse events, and we're kind of doing that in advance of expecting that there'll be some changes to the way the ELSO registry collects the data. Having worked with the current registry chair on moving an equivalent process through the adult ECMO community, but also recognizing that that the ECMO-CENTRAL adverse events are being incorporated into clinical trials of pediatric ECMO right now. So we are adjudicating the ECMO-CENTRAL adverse events for each of our patients in the current kind of ECMO use locally.

Daniel *23:06*
Yeah, I think one of the helpful things I've observed is that, it allows to unearth issues or concerns that may not have reached prominence in the kind of story of the ECMO run, but that deserve attention and may draw our attention to different elements of ECMO care. So it just having, consistency in how we're talking about things, raises the quality of the conversations we're having. When we think about long term outcomes from ECMO there's obviously a lot of work yet to be done, a lot of complexity and understanding the association of ECMO with long term condition for patients exposed to ECMO. Ryan, you're directly furthering our state of understanding here through ASCEND [ARDS in Children and ECMO initiation strategies' impact on Neuro-Development] the prospective observational study of neurodevelopmental outcomes. Can you tell us more? What are you looking for in ASCEND? What do you think the state of our understanding is in terms of neurodevelopmental outcomes after ECMO for kids?

Barbaro *24:10*
Yeah, thanks so much for asking. Pediatric ARDS progresses to the need for ECMO fairly uncommonly. And so we actually needed to have a broad pool of sites to be able to collect this rare event and to help us think about how to optimize care in the future. And so we were able to partner with the ELSO registry and actually embed some of our data collection within the ELSO registry, and leverage the data collection that's already in the ELSO registry to identify and hopefully make more efficient the research of children who go on to ECMO support for pediatric ARDS and then locally as part of the consent process, each site gets the patient's contact information, then at a central site at the University of Michigan, we reach out to each of those family members to follow up what they're doing in terms of their recovery from that event. And those, the choices of the instruments that we ended up using in ASCEND are really designed around aligning with an ongoing clinical trial as well, and that clinical trial was PROSpect [PRone and OScillation Pediatric Clinical Trial]. PROSpect is run jointly by Martha Curley, Martin Kneyber, and Ira Cheifetz. And that study really is looking at whether different strategies of prone positioning the patient prone versus supine, as well as strategies of ventilation, high frequency oscillatory ventilation and conventional mechanical ventilation, discern strategies of care that might be better for our pediatric ARDS patients. But what we're leveraging in ASCEND is the fact that those patients have a protocolized strategy of care leading up to, sometimes ECMO support, and other times, never really reaching ECMO support, And so what we are looking and what we hopefully will be able to clarify, is what's the burden on families, what's the family impact of having survived ECMO support in terms of the way that that impacts daily life. We're also looking at what the quality of life is for children. We get a baseline measure of that that's meant to reflect where they were prior to their illness, and then we follow that out to a year as well, as well as their functional status, and then a measure, another measure, of their fatigue. And so our hope is that when bringing those things together, we'll be

able to see both the trajectory, because we're looking at this at 1, 3, 6, and 12 months of of what that recovery looks like, and where maybe it plateaus, as well as a sense of what the impact of that degree of critical illness is. I often talk about seeing ECMO as an evidence of a big dose of critical illness. You know, what of this is ECMO related, and what of this is critical illness related, and I think that's so hard to tease out. And I think one of the best places, even though it's really aging literature, is the UK neonatal clinical trial. And in that, in that clinical trial, which was published way back now, in 1996 you know, patients were randomized to receive either conventional therapy or ECMO support, in the setting of neonatal related lung disease, and what they did, as well as follow those patients out beyond their hospitalization, and found, really, when they looked at some of those more long term outcomes, that patients in the ECMO and the non ECMO groups had fairly similar outcomes. And I think what that alludes to is that looking at those longer term outcomes among survivors, they didn't find differences for the most part. And when they did, actually, they tended to lean a little bit towards benefits of ECMO. So with that, what I take away from that is at least that we should challenge the idea that all of the adverse events that are happening in our ECMO supportive patients are a consequence of ECMO, and that maybe some of them are more a consequence of the severe, critical illness that we're seeing and might be there regardless of the strategy of care.

Alexander *27:58*
Mela Bembea is doing the Brain Injury Biomarkers of ECMO study, BEAM, with 15 month follow up of all patients. And so that's not multi years, but actually it is longer term than previous, than we previously kind of considered in terms of ECMO outcomes, and our trial of indication based red blood cell transfusion strategy, TITRE, is also has a second primary endpoint of 12 month neurodevelopmental follow up. And so people are recognizing the importance and the value of studying our patient population, not just for survival to hospital discharge, which has been a kind of traditional ECMO metric, but rather for the functional outcomes and neurodevelopmental and cognitive outcomes of our patient population out beyond that kind of 12 month mark. So it's really exciting actually for us to be considering the real consequences of the care that we're delivering. But the other studies are only looking at those patients who receive ECMO, and so to be able to look at the large dose of critical illness in Ryan's population is going to be really interesting. We're all looking forward to the results. When will the results be out Ryan?

Barbaro *29:13*
Study results should be out in 2027 so we still got a little ways to go.

Daniel *29:18*
Well, Dr. Alexander, Dr. Barbaro, you've taken us on a terrific tour of the current challenges and opportunities in pediatric ECMO. Very grateful for your time here today, and I'm sure the global community at OPENPediatrics agrees. So thank you again for sharing your expertise with us here today.

Alexander *29:37*
Thank you.

Barbaro *29:38*
Thank you. This was a lot of fun. Really appreciate the opportunity.

Alexander *29:37*
Thank you.

Voiceover *29:42*
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