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# Pediatric ECMO Cannulation Strategies in Refractory Septic Shock

In this World Shared Practice Forum Podcast, Dr. Graeme MacLaren shares his expert insight on the outcomes of central versus peripheral cannulation techniques for Extracorporeal Membrane Oxygenation (ECMO) in pediatric patients with refractory septic shock as published in the February issue of Pediatric Critical Care Medicine. The discussion focuses on the implications of ECMO modality choices, the conditions affecting cannulation strategy, and how institutional resources can impact patient outcomes.

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# Sarah Marcley 00:04

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# Jeff Burns 00:18

Welcome to the OPENPediatrics Podcast. I'm Dr Jeff Burns, Emeritus Chief of Critical Care at Boston Children's Hospital and Professor of Anesthesia and Pediatrics at Harvard Medical School. We're very pleased to have with us today, Dr Graeme MacLaren. Dr MacLaren is an adult and pediatric intensive care physician at the National University Hospital in Singapore, where he is the Director of the Cardiothoracic Intensive Care Unit and also Associate Professor at the Yu Lu Ling School of Medicine at National University Singapore. Dr MacLaren is also trained as a specialist in infectious disease. He holds a Master of Science in Infectious Disease from the London School of Hygiene and Tropical Medicine. We've invited Dr MacLaren here today to discuss his editorial in the February 10 issue of Pediatric Critical Care Medicine. His editorial is entitled, "Cannulation Strategies for Extracorporeal Membrane Oxygenation in Children with Refractory Septic Shock." In this editorial, he discusses a study that's also reported in the February 10 issue of Pediatric Critical Care Medicine entitled "Central or Peripheral Venoarterial Extracorporeal Membrane Oxygenation for Pediatric Sepsis: Outcomes Comparison in the Extracorporal Life Support Organization Dataset, 2000-2021." Graeme, welcome.

# Graeme MacLaren 01:45

Thanks very much. Jeff, pleasure to be here.

# Jeff Burns 01:48

Graeme, before we start, you know you've written in this area many times. You're the past president of the Extracorporeal Life Support Organization (ELSO) as I said. Could we get clear on how you define peripheral VA support versus central VA support in this context of refractory shock?

# Graeme MacLaren 02:07

Sure. So I think if we look at peripheral ECMO, just to be clear from the beginning, the patient population we're talking about here are children with refractory shock or hemodynamic failure such that they need venoarterial ECMO as part of mechanical circulatory support. So if we accept that premise, then there are only really four arteries you can return the oxygenated blood to. There's the carotid, the femoral, the auxiliary, which is almost never used in children, or the ascending aorta. So with that

framework, I would suggest that peripheral is anything except for the ascending aorta. Classic central ECMO means performing a sternotomy, cannulating the right atrium and the ascending aorta.

#### Jeff Burns 02:56

Graeme, as you know, you trained in Melbourne and at the Melbourne Children's Hospital, they were some of the early pioneers of utilizing VA-ECMO support and shock, and as I understand it at Melbourne Children's Hospital, is it a stepwise approach, where they will attempt peripheral VA-ECMO support in a patient with shock first, before they stepwise to central support, or do they go straight to central support?

## Graeme MacLaren 03:24

Thanks, Jeff. So if we look back in the 1990s they used to try peripheral support first. They used to try and generate higher flows, sometimes by using two venous cannulas. But starting in the early 2000s they generally went to central ECMO first, unless there was a reason not to. Those reasons, for example, might be if the child is off site and needs to be transported in an ambulance, a helicopter or a fixed wing to the children's hospital, obviously doing a sternotomy and then jumping on board a fixed wing is perhaps not the best thing to do. Sometimes in neonatal sepsis, they wouldn't go straight for central cannulation, because I think you can generally get adequate flow using cervical cannulation in newborn sepsis. And then there's a raft of very unusual problems, such as children who have had cardiac surgery before may have extensive mediastinal adhesions, in whom going straight through the chest might not be the most prudent course of action. But in general, they wouldn't cannulate peripherally, watch the child fail that strategy and then scramble to do central cannulation. In general, over the last 20 years, it's been straight to central cannulation in many or most of the children.

#### Jeff Burns 04:43

That's very helpful. Well, I wonder if we could turn now to your editorial and to the study that you were commenting on, as I mentioned earlier. This is a study by Totapally and colleagues from the Division of Pediatric Critical Care at the Vanderbilt University Medical Center in Nashville, Tennessee. And again, this study appeared in the February 10 issue of Pediatric Critical Care Medicine. Graham what questions were Totapally and colleagues trying to answer in this study, and what methodology did they use to answer them?

## Graeme MacLaren 05:15

Yeah, so I think their two key questions was one, is using central cannulation associated with lower mortality than peripheral cannulation. And the second question was, is the use of higher ECMO circuit blood flows associated with lower mortality? And to understand that the context from which these two questions emerged, we need to go back quite a bit of in time. There are still many experienced pediatric clinicians who don't think we should be using ECMO at all for refractory septic shock. Now, in terms of official endorsement in 2017 the American College of Critical Care Medicine put a statement endorsing its use if everything else had failed. The Surviving Sepsis campaign for children, was published in 2020 and that made a similar recommendation, albeit acknowledging the very low quality of evidence. So the question about whether we should be doing it, or the if is still there. So if you allow that in certain circumstances, we should be doing it, then the question becomes, how, if we go far back enough in time, back into the 1990s yet again, sepsis was generally regarded as a contraindication to ECMO. But then we started to see some, some uncontrolled single center case series emerge, generally from North American neonatal units, showing potentially fantastic outcomes. You know, 70%, 80%, 90%

survival to hospital discharge. It wasn't until 2007 that Melbourne published for the second time, their collective experience, which showed there was an association between central cannulation and lower mortality. And then in 2019 a group led by Luregn Schlapbach who was working in Brisbane at the time, but he's now the director of the PICU in Zurich in Switzerland, he put together a lovely study from the Australian New Zealand pediatric intensive care registry, which showed for the first time in several centers, not just Melbourne, for about 80 patients supported on VA-ECMO for refractory septic shock, that outcomes were appeared superior with central ECMO so that was the kind of the background that these group of investigators from Vanderbilt used. And getting back to their two questions they wanted to address, should we be routinely using central cannulation, and should we be targeting higher flows?

#### Jeff Burns 07:43

And Dr MacLaren, what methodology did they pursue to answer this question?

#### Graeme MacLaren 07:48

So they used the registry of the Extracorporeal Life Support Organization [ELSO]. So the ELSO registry has been in place since 1989. It's got more than 230,000 patients in it now, and is arguably the single most important ECMO database that we have available. So they analyzed the last 20 years from ELSO registered centers. And I guess that's one of the strengths of this study, is we're not just talking about one or two centers who have a particular interest in this area. This was real world data. It's International. It's from multiple different centers with multiple different capabilities, and they were able to collate information on over 1,200 patients. Importantly, 30% of them were newborn babies, and they conducted a multi variable logistic regression analysis in an attempt to answer these questions

#### Jeff Burns 08:42

And what did they find? What did they report as the salient findings? And for that matter, what do you think were some of the salient findings?

#### Graeme MacLaren 08:50

I think the key finding was that they were able to demonstrate a statistically significant decrease in hospital survival with the use of peripheral cannulation. The odds ratio for this wasn't particularly large, and the confidence symbols were quite wide. Think the odds ratio was about 1.6. The confidence intervals varied between 1.1 to 2.4 so not an overwhelmingly strong signal, but nonetheless, it did demonstrate there was the signal that that peripheral ECMO was worse than central ECMO in this patient population. I think one of the strengths of this study also is that it's by far the biggest that's ever been done in this patient population, getting 1,200 patients who are being cannulated for refractory septic shock, trounces every other study in literature on this, all of which have had fewer than 100. So the second question about flow data. I think, is harder to interpret, and that's partially because of the limitations of the ELSO registry. So what's collected from the registry is ECMO flow at four hours post cannulation, and at 24 hours. Of course, the registry is relying on volunteers to submit data to them so they can't make it too arduous. They're not having, you know, fully funded professional data collectors most of the time entering this information. So there are limitations to this. And the authors of this study found that that higher flows at four hours were associated with improved outcomes, but not 24 hour flow. So it's a little hard to interpret this one way or the other I think. So I think the flow data is less convincing than the site of cannulation. They also demonstrated that other risk factors for death on their logistic regression analysis were pre-ECMO cardiac arrest and neurological injury, which, as anybody

who looks after this these children knows, of course, that's not surprising, and it has been shown in other studies, these two risk factors predict death.

#### Jeff Burns 10:54

Well, Graeme, you've touched on some of the limitations, but what I found particularly helpful, and undoubtedly the reason that Dr Tasker asked you to write the editorial is, how do you put these findings in context? And most importantly, are these findings generalizable to the wider audience that's listening to us today?

#### Graeme MacLaren 11:12

Well, I think before we talk about the generalizability, we need to look at the study's limitations. I think the first and most important one is that this study didn't have a control group who did not receive ECMO. And of course, again, this is a limitation of the ELSO registry. They're not collecting data on children who were referred but refused or denied ECMO. They were only they only capture information on patients who actually get ECMO. So we can't compare what happened to these children who might have been seen as potential ECMO candidates, but didn't get it. And this is, in fact, one of the strongest weaknesses in all of the ECMO literature. Outside of the few randomized control trials that have been done, in general, we don't know what happens to those who might be ECMO candidates but don't get it, for whatever reason. There's at least two other limitations of this study, and again, the authors acknowledged these, one of which was that the study looked at data over a 20 year period. And as you can imagine, there were guite a few changes in management over that time. And I think one of the most significant, for example, particularly in North America, was the shift from roller pumps to centrifugal pumps, at least outside of the neonatal population. Outside of North America, the uptake of centrifugal pumps was a bit earlier, but perhaps around 2008, 2009 it was only then that North America really made a much stronger shift to centrifugal pumps. Of course, these pumps, they have a learning curve associated with their use, they have different flow characteristics, and this may have affected the results of this study. Another important point again, is that fewer than 10% of the children in this study received central cannulation, and this may be a source of bias, because, as you can imagine, if you work with cardiac surgeons every day, and they buy into this argument that opening a child's chest for central cannulation is a reasonable thing to do. You're probably dealing with a relatively rare institutional setup. Not every center in the world has a pediatric cardiac surgical team who is capable and willing to open the chest of every septic child just because the intensive care physician asks them to. It may be that centers that can facilitate this treatment are more accustomed to dealing with children with this degree of critical illness, so that may be a source of bias. So moving on from the study's limitations, what's my takeaway from this study? Well, I think it depends. It's kind of reinforcing my own bias, which I've been looking after children with septic shock for over 20 years, and I've seen what's happened when you cannulate them peripherally, and I've seen what happened when you get them cannulated centrally by a very experienced surgical team. And it's, it's transformative. The ones who are peripheral ECMO often remain acidotic, shut down with poor cap refill and potential limb ischemia or increased incidence of neurological events, and they remain inotrope dependent, and the flow is often not as much as you would like, versus the central cannulation team. Once they've been properly fluid resuscitated and their coagulopathy has been corrected, then you'll often find them off all inotropes and vasopressors. They're often found, in fact, on intravenous vasodilators such as sodium nitroprusside and all of the problems that you see instead of kind of mottled shut down, acidotic children, the problem seems to be largely over within 12 hours. Now, I realize this is extremely anecdotal, and perhaps won't convince anybody, but I think this study did go some way into on a large

international scale, of suggesting certainly that central cannulation should be at least considered if you're working in a center that has the capabilities of offering central cannulation for a child in refractory septic shock. It should be available for consideration and discussion amongst the senior members of the team. As I said earlier, this isn't for every situation, and even proponents of central cannulation like me wouldn't advocate it for every clinical situation. I think you know if you're working in a center where the cardiac surgical team are obstructive or unwilling or unable to provide the service. Then, of course, that option is off the table. As I mentioned, I generally don't use the strategy in newborns because it's not necessary. And again, because opening a newborn's chest has potential long term consequences, it'd be better perhaps to avoid it. And lastly, again, if they're being cannulated off site and being brought back to your home base, then I would not advocate opening the chest.

#### Jeff Burns 15:50

Graeme, I wonder if we could explore this a little further. As you know, the work by the late Hector Wong and many others had shown that looking at gene expression profiles in ARDS or sepsis. We've known that we've been lumping into ARDS or septic shock everyone together as if they had one driving pathophysiology, and we're now learning, by looking at gene expression profiles that that's not true and that there are different phenotypes. Since the landmark study by Danziger and colleagues in the blue journal now, 45 years ago, the dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome, where they found that patients with ARDS that there was a direct relationship between the delivery of oxygen and the uptake of oxygen. And that led to, as you know, several decades of attempts to augment oxygen delivery to improve outcomes, and by and large, those studies were negative. One could argue that what phenotype fits, what septic shock phenotype is most amenable to, VA-ECMO support. You're the director of the Cardiothoracic Intensive Care Unit, and I don't doubt that you see adult and pediatric patients who have profound ventricular dysfunction. But what do you make of the argument that some make that in the phenotype where there's a profound endotheliopathy, mitochondrial dysfunction, if not uncoupling. That in that phenotype of septic shock, simply delivering more oxygen will not be sufficient that this is a cellular level problem of shock. What do you make of that argument, and in your own practice, do you distinguish between those two driving mechanisms of shock, pure ventricular dysfunction, where further delivery is needed, versus this is a cellular level mechanism that's driving this shock in this particular patient?

#### Graeme MacLaren 17:57

Thanks, Jeff, that's a great question. I think what you're really getting down to here is histotoxic shock, which we normally don't really talk about as one of the classic causes of shock outside of the context of cyanide toxicity. But this, I think we do see this from time to time, generally, an extremely advanced shock. And I agree with you that that it's questionable whether ECMO will address something at a mitochondrial level. I think some of the adult ECMO and sepsis literature may help here. Historically, the use of ECMO for adult septic shock, which obviously is used almost always distributive shock, with an increase in cardiac output, vasoplegia, increase in heart rate, an increase in stroke volume, but a decrease in ejection fraction, was generally seen as having appallingly bad outcomes, which is not surprising. But then a group from La Pitié-Salpêtrière in Paris were able to demonstrate that if you selected your patients properly, then you could get very good outcomes, potentially more than 70% survival at hospital discharge. And this culminated in a paper that they put together. The lead author was Nicolas Bréchot in the Lancet in 2020 which demonstrated that these patients, if they have sepsis induced cardiogenic shock, then their outcomes with ECMO were far better than outcomes without ECMO. So I suspect this is why we see better outcomes in pediatric ECMO for sepsis than most adults,

and I think the reason why is because children, particularly very young children, generally have a greater degree of ventricular dysfunction. We all know that newborns, classically have right heart failure and persistent pulmonary hypertension of the newborn, younger children, perhaps in the toddler age group, may have what used to be called cold shock, which is really an isolated form of left ventricular. or systemic ventricular dysfunction. And it's only when the child gets into adolescence, and we can reliably predict that they will, once they're properly fluid resuscitated, that they'll have distributive shock. And there is actually we conducted a systematic review and meta-analysis. It was 2020, 2021, in the journal Critical Care, which showed this paradox, that if you looked at adult patients, the worse the left ventricular ejection fraction, the better the outcomes were. So all comers had about 30% survival to hospital discharge. But if you can find the analysis to adults with left ventricular ejection fraction of less than 20% then the outcomes rose to more than 60% survival to hospital discharge. So it's very hard to predict at the bedside, I think, who has this form of histotoxic shock that you're referring to, but we can identify patients with impaired pump function, in other words, inadequate cardiac output. And we can do that by a number of mechanisms, all of which are known to this community, direct cardiac output measurements, indirect measurements, through the use of mixed venous or central venous oxygen saturation clinical assessment, of course. So if we have evidence that this patient has sepsis induced myocardial depression, they're more likely to benefit from ECMO.

#### Jeff Burns 20:56

Very helpful. Graeme, I wonder is my last question. If you had to summarize the accumulated literature, and again, you've been investigating this area for a number of decades. You're the past president of ELSO, and you have a great deal of personal experience in your current role as the Director of the Cardiothoracic Intensive Care Unit at NUH in Singapore. What advice would you give for pediatric critical care colleagues around the world on how to think about when to utilize central Veno-Arterial ECMO in the pediatric patient with septic shock?

#### Graeme MacLaren 21:27

Thanks, Jeff, yes. So first of all, the question is, should we be doing this? And to me, the answer is yes, when it becomes necessary. But thankfully, it's very rarely necessary. The next question then becomes how we should do it, and that is institution dependent. It depends on the team. It's not just one individual saying, Oh, I think we should go central or I think we should go peripherally. Obviously, the person who cannulates, which is usually a surgeon, but not necessarily always, will have the final say in the matter. But I think it's important that these things happen at a team level with proper discussion. I've actually been called up by colleagues in the United States before during my morning ward rounds saying, you know, Hi, I've got a child here who I think is dying and would benefit from ECMO, can you talk to my surgeon, he's standing next to me, and tell him that the proposal that I have to cannulate this child centrally is not completely off, you know, off the wall. So that happens. I think, if you haven't done it before, people do feel uncomfortable. They think, you know, why am I opening this child's chest when I could just do, say, percutaneous cannulation of the groin or the neck. But this study by Totapally and colleagues is yet another signal in the literature, and this is at least the third signal, and by far the largest, that central cannulation may be associated with better outcomes. So even if you don't accept that in your own practice, I think you should still at least think about it.

#### Jeff Burns 22:59

And is there a role for peripheral VA support in septic shock in the pediatric patient outside of the newborn with PPHN?

#### Graeme MacLaren 23:09

So as I mentioned earlier in the 1990s RCH used to do that. So peripheral VA-ECMO with two venous cannulas to try and jack the flows up. But unfortunately, if you look at the data, the outcomes were not good. They didn't do any better. So in in very select patients, yeah, it may be a reasonable approach. It may be better than doing no ECMO. Some groups, one Italian group and one group, the Karolinska Institute in Stockholm in Sweden, have demonstrated very respectable outcomes using peripheral Veno-Arterial ECMO in children for septic shock. So I think, you know, we're still at the level of evidence that ECMO needs to be assessed on a case by case basis. It needs to be individualized to the child, and it needs to be seen in the wider context of what institutional resources and experience are available, and I think dogmatically mandating that every child who's septic and who needs ECMO should have his or her chest open, I think that's going too far. But I think there is evidence to support its use, and it should be discussed in each child in whom the need for mechanical circulatory support is being considered.

#### Jeff Burns 24:29

Graeme, this is very helpful. We've been speaking today with Dr. Graeme MacLaren, the Director of the Cardiothoracic Intensive Care Unit at the National University Hospital in Singapore, and the past president of the Extracorporeal Life Support Organization [ELSO] regarding his editorial in the February 10, 2025, issue of Pediatric Critical Care Medicine entitled "Cannulation strategies for Extracorporeal Membrane Oxygenation in children with refractory septic shock." Graham, thanks very much. It's wonderful to be able to speak with an expert in the area, and you're very articulate, and we appreciate all the work that you've done to advance our knowledge of caring for children in this context.

#### Graeme MacLaren 25:12

Thank you, Dr. Burns, it's been a pleasure and a privilege to speak to you. Thank you.

#### Sarah Marcley 25:17

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