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Transplant Challenges in Pediatric Liver Failure

In this OPENPediatrics Podcast episode, Dr. Jeff Burns converses with experts Dr. Akash Deep, Dr. James Squires, and Dr. Barbara Wildhaber about pediatric acute liver failure and the intricacies of deciding when a child is unsuitable for liver transplantation. Discussing insights from their 2024 Lancet Child Health and Adolescent Health paper, they emphasize the importance of a multidisciplinary approach in evaluating clinical, biochemical, psychosocial, and ethical factors. The conversation highlights challenges with exclusion criteria, risks associated with severe multi-organ failure, and the necessity of balancing technical feasibility with overall patient prognosis, while also addressing the ethical implications of organ allocation.

SPEAKERS:

Akash Deep, MD, FRCPCH

Director - Paediatric Intensive Care Unit

and Staff Governor

King's College Hospital, London

Professor in Paediatric Critical Care

King's College London

James Squires, MD, MS

Associate Professor, Pediatrician

UPMC Children's Hospital of Pittsburgh

Barbara Wildhaber, MD

Professor

University Hospitals of Geneva

Chief Physician

Child and Adolescent Surgery

Swiss Pediatric Liver Center

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Sarah Marcley *00:04*
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Jeff Burns *00:18*
Welcome to the 2025 series of OPENPediatrics Podcast. I'm Jeff Burns from Boston Children's Hospital and Harvard Medical School. It's a great privilege to have with us today the authors of a manuscript which appeared in the December 2024, issue of Lancet Child Health and Adolescent Health entitled "pediatric acute liver failure, a multi-disciplinary perspective on when a critically ill child is unsuitable for liver transplantation". With us today are the three senior authors, Professor Akash Deep, director of Pediatric Intensive Care and Staff Governor at King's College Hospital in London, and professor in pediatric critical care at King's College London. Akash, welcome.

Akash Deep *01:03*
Thank you, Jeff, thanks for having us here.

Jeff Burns *01:05*
Also with us is Dr James Squires. Dr Squires is Associate Professor of Pediatrics and the Associate Director of Hepatology at the University of Pittsburgh School of Medicine and UPMC Children's Hospital of Pittsburgh. Dr Squires, welcome.

Jeff Squires *01:20*
Hey, Jeff, thanks for having us. Pleasure to be here.

Jeff Burns *01:23*
And finally, with us today is Dr Barbara Wildhaber. Dr Wildhaber is the Surgical Director of the Swiss Pediatric Liver Center at the University Hospitals of Geneva in Geneva, Switzerland. Dr Wildhaber, welcome.

Barbara Wildhaber *01:37*
Thank you very much. Thank you for having us.

Jeff Burns *01:39*
As I mentioned, the three of you authored a very interesting paper in Lancet Child and Adolescent Health in the December 2024 issue, and it was really what candidates are unsuitable for liver transplantation. So Dr. Deep, if I could start with you, what made you and your authors decide on writing a review on who not to transplant rather than when to transplant?

Akash Deep *02:01*
Thank you. Dr Burns, a very interesting question, but before I answer your question, just I want to give some perspective to our listeners about pediatric liver transplantation. Now we know liver transplantation is indicated for a number of liver conditions, from acute liver failure to chronic to metabolic to intoxications and of all the indications for transplant in a child, acute liver failure constitutes about 10 to 20% of these indications. But if you look at the listing criteria for pediatric acute liver failure, that has always been a challenge, because the routine ICU scoring systems like the PIM [Pediatric Index of Mortality], the PRISM, [Pediatric Risk of Mortality], the PELOD [Pediatric Logistic Organ Dysfunction], they do not apply for patients with acute liver failure. The other scoring systems, like the King's College criteria, they are not fully validated. But what we observed as a team was that the biggest conundrum for the treating teams come when the decision of not to list a patient for liver transplantation comes, or when we have to discuss, when is a liver transplantation deemed futile for a child? If you look at statistics, approximately 10% of critically ill children liver transplantation is deemed unsuitable. The reasons could be the child is too unwell, or the underlying cause might carry a poor prognosis. There could be others, like social, logistical and ethical kind of considerations as well. So we as a group were quite intrigued to see that there was very little literature on this subject. So with the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) we first organized a webinar on this subject. And we were amazed to see the interest. We were amazed to look at the discussion which went around various aspects. And that's when we gathered a multidisciplinary team to write a review on this important but controversial topic. And what we wanted to emphasize was that too sick to transplantation is just one part of unsuitability for transplantation. There are many others. So when a child becomes too unwell, liver transplantation can cause perioperative morbidity and mortality, but we also need to remember the graft wasted which goes with it, and that is detrimental for the others who are on the waiting list. And if you look at the donor liver scarcity, that should automatically prompt a holistic evaluation on who should get the transplantation. And that's what we have done in this review, we've explored from a multidisciplinary perspective, why and when a critically unwell child with acute liver failure might be unsuitable for liver transplantation.

Jeff Burns *04:37*
Akash, thank you for that. My next question concerns really exclusion criteria, because, as you pointed out, we're used to seeing established inclusion criteria, but there are difficulties with establishing exclusion criteria. From the ICU standpoint, what are some of those?

Akash Deep *04:54*
Thank you. Dr Burns, again, a very interesting question, and that brings us to what kind of a disease is acute level of failure. It's a dynamic disease, and it's a very rapid downhill course it takes. So the

parameters on day one will not necessarily predict mortality, futility or the need for transplantation. Therefore the models, whichever model we use, needs to mirror this dynamic course. And second important thing from an ICU perspective, is the predictive utility of the models that incorporate multiple factors, whether it's biochemical, whether it's clinical, they get hampered by the interventions which we aim to optimize the care. For example, if you take hyperammonemia as an indication for starting CRRT for hyperammonemia, that's going to artificially bring your ammonia down, that will also artificially bring your bilirubin down, which means we cannot use these biochemical parameters in the predictive models. And third important thing is that a lot of these models have clumped the need for transplantation and death into one bucket, and which might or might not be true. So I would actually ask Dr Squires, one of our co-authors, to comment on what the listing criteria are, so we can clump the exclusion and the inclusion criteria together.

Jeff Burns *06:09*
Dr Squires, as a hepatologist, let me pick up on what Akash was just saying. What are the various clinical, biochemical and other factors that you consider before listing a patient for a liver transplant. And of course, we're talking about pediatric patients with acute liver failure.

Jeff Squires *06:24*
Right, and yeah, I think for the listeners, it's, you know, it's going to be important to try. No, we're likely going to toggle back and forth between listing and then not listing. And so I think that's kind of one of the important distinctions to kind of make sure that we try to keep straight as we have these discussions. But as noted, you know that the quote, unquote listing criteria really don't exist either, right? What does exist is a research definition of pediatric acute liver failure. And I say it's a research definition, it has been generally, kind of adapted as a clinical definition. But, if you understand the origins of it, and here I'm talking about, you know, the child without any known liver disease, a coagulation based disorder where the INR is either above 1.5 with encephalopathy or above two without encephalopathy, and again happy to kind of expand on the origins of this definition that is not correctable by vitamin K. But this definition was essentially developed for the kind of pediatric acute liver failure Study Group, which was an NIH based study that I think many of the listeners may be familiar with as it relates to some of the outputs that that study did over the late 90s and early aughts. But what that definition wanted to do was recognize a child who was at risk for decompensation from liver disease and would be in need of liver transplant. That definition has now been generally adopted to become a definition whereby it is used clinically to assign a diagnosis of acute liver failure, and many will use that definition, or, you know, kind of that threshold to consider listing for liver transplants. I think, as Dr. Deep has been talking about a little bit, is that just because you reach a threshold of acute liver failure does not mean that you should immediately be listed for liver transplant. And there has been a lot of work done to try to figure out how we can predict those kids who do meet that definition, who will need a liver transplant and who will not. And again, there are many shortcomings with the multiple prognostic factors that are out there. But to specifically address your question of, you know, when would we consider listing a child for liver transplant? You know, I think clearly if they meet the definition of acute liver failure. You know, we would begin discussions about whether or not this child needs to be listed. I think these discussions, as is noted by the authorship of the paper, needs to happen with the multiple care teams of people involved of these child, generally in the ICU. I think we will generally use some of those kind of clinical markers that have come out in the multiple kind of prognostic markers. So again, the development and progression of hepatic encephalopathy, bilirubin that is rising, and INR that is rising. But none of these, in isolation or even together, are clear kind of red lines for when a child

needs to be listed. And I think at the end of the day, you know, a good clinical exam and frequent touch points with the multiple care providers that are caring for the child, and really kind of keen decision on whether or not this child is suitable for transplant is probably the best path forward.

Jeff Burns *09:33*
And so Jim to build on that, could you take us through those etiologies where you would be wary of listing a critically ill patient for liver transplant.

Jeff Squires *09:43*
Sure. And you know, again, I think in the paper, we have a one of the tables that kind of looks at, you know, kind of the absolute and relative contraindications for transplant. And I think it's important to recognize that this, in and of itself, is really a moving target, right? I think if you go back to, you know, some of the earlier papers that looks are kind of complete contraindications for liver transplants, many people will consider things like mitochondrial hepatopathy as a kind of, you know, universal contraindication for transplant. That said, there are now kind of, again, small series, small reports, no large data, but we're dealing with rare diseases here that do show that that in some of these populations, transplant may have a role, you know, I think the child, for example, you know, with DGUOK, who has isolated, kind of, you know, hepatic manifestations of their disease. And so, you know, TRMU is another mitochondrial disease where there, you know, some of the literature suggests that there is some good outcomes. And so I think it's important to recognize that even though we may talk about relative and absolute contraindications, there still may be exceptions to all of these rules. I think clearly a child who presents as a manifestation of acute liver failure with extra hepatic malignancy would be something that would be very reluctant to take back to the OR. I think uncontrolled infection is one where you know, we would absolutely want to try to get that under control before moving forward with transplant. You know, things like Niemann-Pick disease and again, some of the more severe mitochondrial diseases. These are diseases where, really, would, you know, likely suggest, with the data that we have, that the liver transplant would not be in the best interest of this child. I think you know some of the diseases like HLH or Hemophagocytic Lymphohistiocytosis. This is another where, I think has been classically considered, you know, a contraindication. But as we see more and more data coming out, there may be certain populations that that do see a benefit from transplant. So again, every child is different. Every child deserves an opportunity to have a discussion about whether transplant would be in the best interest of that child. And I think that those, those discussions are critically important before making final decisions.

Jeff Burns *11:50*
Thanks, Jim. Akash, can I take it back to you from an ICU perspective? What are the key factors which might make a child non-transplantable?

Akash Deep *12:00*
As an intensivist the first thing we need to understand is, why do children die when they have acute liver failure? It's multifactorial. We talk about cellular edema, with raised intracranial pressure. We talked about uncontrolled sepsis, and we talk about multi organ failure. So therefore we are very closely monitoring these children with non-invasive neuro monitoring, whether it is transplant Dopplers or optic nerve sheath, and if we have a child who's got refractory raised ICP despite all the measures, or has got pupillary changes, for example, so one has to very carefully then discuss this patient with the multidisciplinary team before listing or subjecting this child to liver transplantation. Now, similarly, for

example, if this child is on high frequency ventilation or on a very high PEEP, again, we know that it's going to be very difficult for the anesthetists to kind of maintain this child on that kind of pressures in the OR. Then we come to uncontrolled sepsis. We know that the risk of sepsis is very high in ALF because the anti-inflammatory response to liver injury will result in functional monocyte deactivation. So we need to control sepsis. We need to control this disseminated infection before we say we're going to subject this child to transplantation. And finally, we talk about multi organ failure. So what are those parameters as an intensivist, which will raise the alarm bells. And that is where it when you are on very high multiple vasoactive agents, when you're on very high ventilatory pressures or FiO2 requirements. You've got refractory raised intracranial pressure, you've got complete dependence on CRRT or on plasma exchange. So all these factors need to be considered. We are not saying that when these children are in multi system organ failure as a contraindication, but we need to assess all these factors to see whether the child is going to survive the process of liver transplantation. And here, I would like to mention extraordinarily there are some patients who've got reversible, and I want to stress the word reversible, severe acute respiratory or cardiorespiratory failure, we have who have been bridged to liver transplantation after receiving ECMO. So we had a patient, for example, at King's who had Wilson's, was on three inotropes, was on almost 100% oxygen, raised ICP, and after multiple multidisciplinary meetings, we said, probably this child might come out of the woods. So we gave this child pre-transplant, intra-transplant and post-transplant ECMO and the child survived with intact neurology. But for a second, I'm not saying that every child who has got this refractory multi organ failure should be put on ECMO. It has to be case by case discussion, and a multi-disciplinary team has to agree that it's a reversible cardiorespiratory failure, and the child will survive the process. So if I have to summarize what the intensivists look at, we look at the reversibility and the severity of end organ failure. We look at how severe the hepatic encephalopathy is. But what we need to mention here is that the paradigm is changing, which means that the need for mechanical ventilation, for severe ARDS, vasopressor support, renal replacement therapy should not preclude liver transplantation in isolation, but it has to be weighted alongside the overall probability of the patient surviving liver transplantation in short and long term.

Jeff Burns *15:21*
And Akash, you and Dr. Squires as a hepatologist, have both noted it's a multi-disciplinary decision, because you need all of that wisdom to try to understand, is this patient an optimal candidate? With that said, what are the considerations that our anesthesia colleagues are thinking about trying to weigh whether a patient should be transplanted or not?

Akash Deep *15:42*
Very interesting question, Jeff. it's we are to remember that anesthesia and ICU are very closely interwoven. The anesthetists need a very calculated risk assessment to balance what will happen in the OR because of the surgical stress, the bleeding, the reperfusion injury against the organ reserve and dysfunction. They come to us, we sit down together and say, right, these are the ventilatory pressures. These are the vasoactive support we have. And this is the child is dependent on renal replacement therapy, and that is where the second call comes then to say, right, I'm going to disconnect this patient from the big ICU ventilator and put on a portable ventilator. What kind of decompensation am I expecting? This child is on CRRT for three days, has got ammonias of 200, very high ICP. How am I going to manage this patient intraoperatively? Does this patient require intraoperative CRRT, and that's what we have started to do at King's quite often. It's a it's again, a shared decision making between ICU and anesthetists, because that requires staff, that requires training, and we just need to make sure that

CRRT is available if, as a team, we feel that that that's what the patient requires. So in summary, understanding the ICU support being provided and the physiological reserve of a child before being transferred to the OR is very crucial, and that is done by the anesthetist in conjunction with the intensivist.

Jeff Burns *17:09*
Well, Dr. Barbara Wildhaber, you're the Surgical Director of the Swiss Pediatric Liver Center. And so could you give us your perspective on this very difficult decision? Obviously, there are size and donor considerations, but what are the factors that you're thinking about when you're brought into this discussion with a child who's got acute liver failure, they're critically ill, and you're trying to weigh, are they a candidate or not?

Barbara Wildhaber *17:35*
Thank you for this question. It's true, the surgeon, very often is called a little bit later on and not from the beginning. And as a surgeon, I'm very technical, but on the other side, I feel that we have to see at the child in a very holistic way. And our discussion is quite technical right now, and I do always think about what's feasible and what's reasonable. And because as a surgeon, I'm expected to do everything. We are expected to do anastomosis in two millimeter vessels, and we are we are supposed to do whatever we expected to do. And the feasibility we can always respond with, yes, we can do it. But my question is always, is it reasonable to do this? And I think we will talk about this later, about ethical issues, social issues, family issues and hope and whatever comes with liver transplantation and graft survival, but when it comes to very technical issues in surgery, I think we can say, nowadays, we can do it. We can do very small children. There's no cutoff where you say, I don't do this child because it's a 1.7 kilogram child. But there must be a limit, also to what you as a surgeon, you are able to do. What is your experience? What is your limit of yourself? Because never, ever do we want to lose the child with its graft after liver transplantation or during liver transplantation. So yes, size may matter, because the smaller child, the more difficult is a liver transplantation. Surgical challenges are very big, with small vessels and fragility of the tissue. And then we have to have a good, suitable organ which gives us the good size for the child, because the higher the recipient to graft, a weight ratio is, the more we are in danger that we have volume problems with anesthesiologists, and the child will not have a good profusion of the tissues and the liver and so on. And there's the bleeding issue. I know that this is also an anesthesiology logistical issue, but bleeding is coming with liver transplantation as the aggression we give to the body of the small child, and then bleeding is coming with also we have to give anticoagulation in a small child or in difficult anastomosis, because we do have to prevent thrombosis, and then you have, again the risk of bleeding. And so this balance between thrombosis and bleeding and anticoagulation is something we do have to consider, together with also the maturity of the brain, with the age and the fragility and the frailty of the patient. So there are many issues, but actually there's no news from the surgical side. Because again, technically, I think nowadays, with what we have, with the help we have from everybody, we can do it, but we have to think, is it reasonable?

Jeff Burns *20:29*
Dr. Wildhaber, I would imagine that with the increased specialization in your field, and in particular with living related transplant and even segmental transplants for the smaller child and infant, this has really changed in so many ways, your perspective on what is possible, is that so?

Barbara Wildhaber *20:52*

I think it extended our possibilities. And thank you for that question, because it's true that now, even in with a mono segment and with a very, very small graft, we can do transplantation, but it comes with more risks, and we need to be aware again that what is feasible of splitting a liver in one segment and giving a 90 gram liver to a small child is possible and feasible, but it comes with its price. It comes with a lot, with maybe more bleeding. It can come with more thrombosis. It comes with its risks, and this we have to put in the balance when we decide altogether, is a child suitable for liver transplantation. Not only is liver transplantation suitable for a child, because both considerations are very important.

Jeff Burns *21:38*
Well, Akash, both our colleagues here have mentioned that this is of course well beyond the technical considerations. That there's the family perspective, and then there's the ethical dimension of should we potentially sacrifice a graft if the odds are really against success here? How do you think about these issues?

Akash Deep *21:58*
I think both my surgical and Hepatology colleagues have very rightly said that it's not just a technical pitch. It's not about just how sick the patient is, because that's just one dimension of when do you think the child is unsuitable for liver transplant? There are factors like the social factors, the psychosocial factors, very importantly, the logistics involved in liver transplantation and the ethical considerations. I'm going to give you some examples of how we think these factors interplay into each other. If you look at a high income country, probably, not all, but all these patients who have acute liver failure, who we deem to be suitable for liver transplantation, probably will be able to access one. But if you look at organ availability on a global level that's strikingly very varied. Not every medical system will be able to provide liver transplantation facilities. And not every ICU will be able to manage these really sick, unwell children. The poverty, the ability of the patient's family to pay for post transplantation immunosuppression, again, very, very important. And that leads us to a question, would a liver transplantation be justified for a child whose family cannot afford immunosuppression? Similarly, if you look at the psychosocial considerations, adherence to your post liver transplantation immunosuppression regimens really challenging, especially in teenagers. So I'm going to give you a hypothetical case. Look at a teenager who's required liver transplantation after an intentional drug overdose. It's precipitated acute liver failure. The child has got a liver transplantation, but subsequently, after a year, presents with a further overdose and a failure of the grafted liver. So here is where the psychosocial evaluation of the probable quality of life, or the chance of the recurrence of the same event has to be very carefully weighed against the risks and benefits of a second liver transplant. I'll give you a second example of another teenager who's got diabetes and in the last six months has presented 4, 5, 6 times to the OR with non-compliance to insulin. Now this patient has developed acute liver failure. Where are we justified? How are we justified that this patient is going to adhere to the post transplantation immunosuppression protocols? And then, as you rightly said, Dr Burns about ethical consideration. Absolutely fundamental when it comes to evaluating children who are suitable or not for listing for transplantation, where it is due to the physiologic futility for liver transplantation or an overwhelming risk of not surviving long after liver transplantation. Ethicists play a very important role here, and these are all very tricky decisions we've all seen. You've got a child who's got acute liver failure, who's got refractory multi organ failure, versus a child on the next bed who is relatively less sick. You've got one donor organ. How do you allocate the organ, and which patient should this organ go to? I think, in summary, it has to be a multi-disciplinary approach. Yes, we talk about thickness. Yes, we talk about technical aspects. We talk about overall prognosis, but the social, the ethical bits have to be

considered in each and every patient, and there's multi dimensionality of the moral conflict, and this emphasizes the importance of shared decision making.

Jeff Burns *25:35*
Well, we have with us three senior investigators from this paper in the 2024 December issue of Lancet Child Health and Disease. And also not just investigators, but clinicians who lead their transplant programs at their various centers. Dr. Wildhaber, could I begin with you at the Swiss Pediatric Liver Transplant program in Geneva? What would be the process for listing these complex patients?

Barbara Wildhaber *26:03*
If we have a patient we need to list, we have first to go to a local committee, which has to look at the chart and has to look at the summary we present. Because we first need an objective evaluation by somebody who does not know the patient nor the family. I do think that very important, because very often with our children, we are taken by emotions as well. And again, the family is part of the team, and we may be taken by the family and be influenced by the family. So that's the first step, there's an objective evaluation. And then we go with this, after this evaluation, we go to the super urgent listing in our organization in Switzerland, which is called Swiss Transplant, which is a [inaudible] organization, and then we can list this patient at the first position as an urgent status. We have just urgent status in Switzerland, or no urgent status. And we can go to urgent status that works. Is really nice in Switzerland. We collaborate with France. And so even in France, we can list it at the first position. And so we actually with this process, we very often, and I cannot say always, but very often, get the liver within some days, so which means we have a very low mortality on the wait list and super urgent list.

Jeff Burns *27:19*
Thank you, Dr Wildhaber and Dr Squires, as I mentioned earlier, you're at the University of Pittsburgh Medical Center. Probably in the United States, arguably, easily, one of the most experienced liver transplant centers, certainly for adult and equally for children. What would be the process for listing a very critically ill patient with acute liver failure, where you're questioning whether we should do this or not? What would be that process in Pittsburgh?

Jeff Squires *27:47*
You know, again, I mean, I think as soon as these patients hit the door, they are often in the ICU. Hepatology is often already involved, you know, in here in the United States, at least in Pittsburgh and other places that I've trained and worked at, you know, oftentimes the transplant hepatologist and the transplant surgeon are on rounds at the same time, you know, kind of with the patients in the hospital. And so oftentimes those conversations are happening right away. You know that there's a patient in the hospital who you know has acute liver failure and may need transplant. And so I think ultimately, you know these discussions, we keep saying multi-disciplinary, but again, they're multi-disciplinary. And I think the ICU, the hepatologist, the surgeons, are probably the three main ones initially that determine whether or not we should feel like we should move forward with listing for liver transplants. As Barbara kind of mentioned the urgent status in Sweden, I think many of the listeners in the United States will recognize the allocation system here in the US. You know, once these patients are deemed suitable for transplant and are listed for transplant, they then go to the Status 1A, which is our highest status here in the United States, for listing. And so again, kind of go near or at the top of the transplant list, and that's across the entire United States. And so, you know, I think the process is conversations that happen very quickly and at all hours of the day. Once the kind of collective decision to list is made, the

patient still needs to go through a complete evaluation. And so this includes assessments by the multi-disciplinary team that includes surgery, anesthesia, infectious disease, obviously transplant surgery, and then collectively, those those folks weigh in on whether or not this patient is deemed suitable for listing, and if the collective thinks that they are, they get listed and go straight to the top.

Jeff Burns *29:39*
And Dr. Deep what would be the process at King's College in London.

Akash Deep *29:43*
Thank you, Jeff, as my colleagues have mentioned, it's a multi-disciplinary approach, but in the UK, we are very uniquely placed that we've got only three liver transplant centers in the whole of UK. We've got Kings College in London, Birmingham Children's and Leeds. So once a patient is deemed a candidate for liver transplantation, there's a multidisciplinary meeting which takes place within that Institute, and a decision is made, yes for transplantation, and then we use the NHSBT, which is National Health Service Blood and Transplantation criteria for super urgent listing of these patients. So the patient then gets super urgently listed, and any liver in the country which becomes available then gets offered to this patient who's on the super urgent list. But again, you might have a child who is super urgently listed, but then develops a contraindication, then develops a problem, and then we again come back as an MD to say, do we need to keep this child on the list, or is it worth temporarily suspending this patient and come back and re-list the patient? So these are decisions which are made on an ongoing basis in a dynamic way, and live in time, rather than just making one decision and then not revisiting it.

Jeff Burns *30:54*
Thank you. We've been discussing today the manuscript "Pediatric acute liver failure, a multi-disciplinary perspective on when a critically ill child is unsuitable for liver transplantation", that appeared in the December 2024 issue of Lancet Child Health and Child and Adolescent Health with the senior investigators, Doctors Deep, Squires and Wildhaber. I thank the three of you for being with us today, this is a very interesting and eye opening perspective. And I think the way that you presented your manuscript provides clear guidelines for research in your field, because you're pointing out where we are at the apparent limits, at least as exists in 2024 and 2025 and it's a great contribution to the literature. So thank you for being with us on the OPENPediatrics podcast.

Akash Deep *31:39*
Thank you for having us.

Barbara Wildhaber *31:41*
Thank you very much.

Jeff Squires *31:42*
Thanks everybody. It's been a pleasure.

Sarah Marcley *31:44*
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