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Insights from the PRESSURE Trial

In this OPENPediatrics World Shared Practice Forum podcast, Dr. Jeff Burns and Dr. David Inwald discuss the findings of the PRESSURE randomized clinical trial. Recently published in JAMA, the trial evaluated permissive blood pressure targets for critically ill children receiving mechanical ventilation and vasoactive support compared to usual care. Dr. Inwald reviews the rationale that prompted the study, summarizes the primary and secondary outcomes, and discusses clinical implications of the findings. The speakers also explore how these results may influence hemodynamic management and evidence-based decision-making across diverse healthcare settings.

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Sarah Marcley *00:04*
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Jeff Burns *00:18*
Welcome to OPENPediatrics World Shared Practice Forum podcast. I'm Dr. Jeff Burns from Boston Children's Hospital at Harvard Medical School, and I am very pleased to have with us today Dr. David P. Inwald. Dr. Inwald is the first author of the recently published article in JAMA on September 28, 2026, published online ahead of print for their clinical trial "Permissive Blood Pressure Targets in Pediatric Critical Care: The PRESSURE Randomized Clinical Trial." I might also add that this was presented live at the 13th World Congress of the World Federation of Pediatric Intensive and Critical Care Societies at Melbourne, Australia, on September 28th at noon Melbourne time, David presented this. It was a very large audience. I was very fortunate to be in the audience as he presented the findings in real time, and you could have heard a pin drop in the room. So, David, welcome to the OPENPediatrics World Shared Practice Forum podcast. Thank you, Jeff. Lovely to be here. David. I know that you've you were affiliated with several hospitals in the UK, and then you transitioned several years ago. Could you just briefly, for our audience, identify your professional affiliations over the last 15 or 20 years?

David Inwald *01:37*
Sure. So I'm David Inwald. I'm the I'm a pediatric intensivist, a clinical pediatric intensivist, though I have had academic affiliations and I'm a clinical trialist. I've been a consultant, which I guess is a equivalent to a senior attending at St. Mary's Hospital in London for 15 years. Then I moved to Cambridge just before COVID, and I've recently stepped down from NHS practice. I'm currently working in a private hospital in London clinically. I also have an affiliation with Cambridge University, where I teach first year undergraduates physiology.

Jeff Burns *02:11*
One of my favorite topics to teach medical students, residents, and fellows as well. David, you've been very active in the UK Pediatric Critical Care Society study group for many many years, and I just briefly want to say that the work coming out of of your research consortium is simply is simply terrific. It's got scientific rigor. It's generalizable across all resource environments because, in my view, you're you're testing very fundamental questions. You know, the lower limit of of oxygen saturation, in this case, a

lower threshold for blood pressure. Could you first, before we talk about the findings of the study, could we go back and first, what was the question you were seeking to answer in this study, and what was the preliminary data that informed your study design? That this was something that should be tested.

David Inwald *03:04*
Sure, I mean I think in terms of the UK current clinical trials architecture, I think we're incredibly lucky, as you say, to work in a very collaborative environment with a great group of clinicians who work well together and want to answer questions, and that all works quite well with the with the structures that are in the UK to support research. In terms of the particular question that we were looking to answer in the PRESSURE study, we were really looking to ask the question about what is a reasonable blood pressure to aim at in pediatric intensive care. Really, because there was very little data in terms of clinical trial data to support current practice, so that was our main aim: was to try and work out, or to try and develop an evidence base upon which to base practice, given the lack of clinical trials in the area up to now. So, in terms of preliminary data, we had done quite a lot of work in the years preceding the trial, looking at blood pressure measurements, blood pressure targets in UK pediatric intensive care units, and we'd published a couple of observational studies looking at observed blood pressure measurements in a number of different pediatric ICUs, and seen that the observed mean blood pressure, mean arterial pressures were probably around the 50th centile for age, something like that. And this was clearly in a recent population and undifferentiated, and included extubated patients as well as those intubated. So difficult to draw any major conclusions from that, other than to say, well, we do seem to be hitting MAPs [Mean Arterial Pressure], possibly in excess of where you might imagine they might be in a pediatric critical care population. We also spent some time looking at invasive versus non-invasive blood pressure monitoring, and then we did a small survey that was unpublished, asking clinicians the question: Well, what MAP are you targeting in your patients who are on vasoactive drugs in the PICU. And the answer was somewhere between the fifth and 50th centile. So that seemed to be usual practice. Now this was obviously a survey done some time ago now because the PRESSURE study started recruitment in 2021, and there was obviously a period where we were building the study and getting funding, so the survey I think was actually back in, I think 2018 or even 2019. I can't remember now, but that was the practice at the time. So it seemed to be the case that people were targeting a MAP somewhere between fifth and 50th centile, or simply more towards the 50th. That was reasonably common practice at that time, and at the same time, we knew from the data that was around from clinical trials, there was really very little data at all from clinical trials. In fact, none. And when we wrote the surviving sepsis campaign guidelines, I was chair of the hemodynamic section for that. We could really not make any recommendation about whether or not fifth or 50th centile should be targeted, and it was identified that this was an area that was ripe for clinical trials. So really, all that data together led us to think that a pediatric critical care trial looking at permissive blood pressure targets would be something very useful. At the same time, there was emerging data from the adult side of critical care that permissive blood pressure targets appeared to be potentially of some benefit in particularly older adults with septic shock. And again, this was more data supporting a kind of less is more strategy, if you like, in pediatric critical care or in critical care in general, which we thought might be extended to pediatric critical care.

Jeff Burns *06:45*
And once again, folks were speaking with Dr. David Inwald, the first author on the recently published clinical trial entitled "Permissive Blood Pressure Targets in Pediatric Critical Care: The PRESSURE Randomized Clinical Trial," published online on September 28, 2026, in the Journal of the American

Medical Association (JAMA). David, can you briefly describe the study design and the interventions in this clinical trial?

David Inwald *07:11*
So this was a pragmatic, multi center, unblinded, individual, randomized clinical trial. That was the study design, and what we were comparing was a permissive MAP target strategy, where we were aiming to target a MAP just above the fifth centile for age, knowing that the fifth centile really defines hypotension. So we didn't want to make patients hypotensive. We were trying to get just above that range. So it was kind of the lower end of normal for age, if you like, or fifth centile versus usual care, and the reason we decided to go for a usual care strategy is because we knew from our the scut work we'd done with a survey that usual care was generally not to target a very high MAP centile such as 50th or above, and we wanted to compare intervention to something that was happening in real-world practice. We didn't want to give people a comparator that would force them to maybe give interventions that were over and above what they would normally be doing in their critical care practice.

Jeff Burns *08:14*
And David, you well described the study design, the major inclusion and exclusion criteria for this population that you studied.

David Inwald *08:21*
So we were interested in the population of children who were invasively mechanically ventilated on vasoactive drugs. So it was basically children, and then they had to be enrolled within six hours of hitting all the inclusion criteria, which included either being accepted or admitted to a participating ICU. And we said accepted because we wanted retrieval teams to be involved in the study. We were encouraging patients to to be recruited by retrieval teams prior to admission to PICU. So they had to had face to face contact with PICU staff or a transport team on invasive mechanical ventilation on a continuous infusion of vasoactive drug, and that drug was expected to continue for at least six hours, so there was a kind of six-hour window from hitting all those criteria to randomize the patient into the study, and then in terms of exclusion criteria, really these we excluded populations where there was a lack of clinical equipoise. So these included patients post cardiac surgery or with some cardiac diagnoses, we also had a neurological exclusion criterion, which we called acute brain injury, and this was really operationalized to mean any patient in whom there was a clinical concern about cerebral perfusion. So, for example, any child with a traumatic brain injury or with evolving cerebral edema, patients who maybe were post-cardiac arrest, and there was concern about outcome because of cerebral perfusion. These were patients that clinicians were empowered to exclude, and then there are a couple of other exclusions, including conditions where you would aim for a higher blood pressure, such as pulmonary hypertension or underlying hypertension. Death was perceived as imminent, or if the patient was previously recruited to the study.

Jeff Burns *10:04*
That's obviously very helpful for our listeners to know whether the findings that you're about to reveal are generalizable to their populations, or which populations that they care for are these findings potentially salient. And David, as I mentioned, the room was full when you presented this on September 28th at Melbourne, and it was simultaneously published by JAMA. So, what were your salient findings?

David Inwald *10:29*

So, thinking about the primary outcome, our primary outcome measure was a, I guess, a clinical effectiveness primary outcome, a composite of death and ventilator support at 30 days. So, it's probably important just to understand that before we come on to the main finding. So this was a an ordinal outcome measure between one and 31, where death was classified as the worst outcome and scored 31. Otherwise, n was the number of days of ventilation at 30 days. And there were a number of secondary outcomes as well that maybe we can talk about in a moment. But in terms of the primary clinical outcome measure, which was this composite of a death and ventilated support at 30 days, the finding was is that we didn't find any significant difference between the intervention arm and the control arm, and we used probabilistic index to look at that. So we found the probabilistic index was 0.52, but the confidence intervals were below, above, and below 0.5, meaning that there was not a significant effect. So we didn't find a significant benefit of the permissive MAP target in terms of the primary clinical outcome measure that we developed, and that came out with a p value of 0.23.

Jeff Burns *11:39*
And your secondary outcomes.

David Inwald *11:41*
So, in terms of secondary outcomes, again, you know, when we publish these things in a journal such as JAMA, we have to be careful about the language we use. And there was no significant difference in the secondary outcome measures between the permissive MAP target group and the usual care group, other than there was a reduced PICU length of stay in survivors in the permissive MAP target group, so 159 hours versus 166 hours, which just came out as significant with a probabilistic index of 0.53, with confidence intervals of 0.5 to 0.56. So that came out as significant. Having said that, I think given that this is a podcast, we can say that in actual fact, if you look at the point estimates, all of the point estimates were towards benefit, even though they didn't come out as significantly different when a statistical test was applied. But you know, all of them were in the direction of benefit if you just looked at the point estimates. And that would be if you looked at time to liberation from ventilation or mortality at discharge and so on. There are a number of other secondary outcomes as well that I'm not going to describe all of them, but those were I think the really important ones.

Jeff Burns *12:55*
And David, you know, this is a very complex trial, and as you're noting, the the findings are also subtle. Are there any other secondary outcomes that you'd like to discuss?

David Inwald *13:05*
Yeah, so we looked at receipt of renal replacement therapy because obviously that's great interest to clinicians, particularly if you're pursuing a permissive MAP target strategy. And we found no difference between the permissive MAP target group and the usual care group, either in survivors or non-survivors. So, you know, survivors, I think there was about seven to 8% incidence in renal replacement therapy in non-survivors, about 25 to 27% and that was similar in both groups, so that provided some reassurance. In terms of sub-group analyses, again, no significant difference in mortality between the permissive MAP target group and the usual care group. Although, again, some of the point estimates towards benefit in the permissive MAP target group in some of the subgroups.

Jeff Burns *13:54*

And David, I'm sure our colleagues around the world who are listening to this would like to know whether there were any adverse events in conducting this trial.

David Inwald *14:04*
Yeah, that's a really good question, Jeff. And I think we were very careful to make sure that we had a a number of adverse events that we defined as expected. So there was really compulsory reporting if any of these adverse events occurred in any of the patients on the study, and these included events that might be evidence of impaired tissue perfusion, like myocardial ischemia, cerebral ischemia, acute kidney injury. We also looked at some other aspects, such as central line-associated bloodstream infections, central line-related thrombosis, arrhythmia, and skin necrosis and so on. Given that we know that many of these vasoactive agents require the insertion of central venous lines, and in actual fact, we saw no significant difference in the overall rate of adverse these these expected adverse adverse events in the permissive versus usual care group. And when we looked in granular detail at some of the things that I'm sure people would want to know about, such as myocardial ischemia, acute kidney injury, acute cerebral ischemia, there's really no difference between the groups. So I think that provided great reassurance that, in terms of safety, the intervention was not posing any harm to patients, and that was very important for us to demonstrate.

Jeff Burns *15:22*
That was terrific, Dr. David Inwald. As you know, JAMA asked for an editorial of these findings as another indicator of how important this study was that you conducted and are the first author of. And Chris Horvat and colleagues published the editorial. And allow me to read one of the summary quotes from their editorial. It goes like this: "the trial provides reassuring evidence that vasoactive infusions can be weaned earlier than the typical practice in usual care because shock is resolving. It provides comparatively little evidence regarding the safety of a fifth percentile floor in a very critically ill child with hypotension. The trial is currently collecting 12 month follow up data, which may shed light on whether other end organ outcomes related to blood pressure management should further guide practice." How do you respond to that quote, and how would you interpret that kind of summary of your clinical trial?

David Inwald *16:20*
Yes, thank you very much for the question, Jeff. So I think it's a reasonable criticism that we showed safety of the intervention that is the fifth centile MAP target, just as it was delivered and not as it was intended. And that's because there were some deviations, meaning particularly for the younger age categories, the permissive MAP target wasn't strictly achieved, and the longer term outcomes may be helpful to look at, but remember these are just quality of life measurements rather than a detailed neurodevelopmental assessment. But I think we've already shown no signal for harm, and there's no difference in functional status between the groups before and after PICU admission. And I would also say a demand for very tight adherence to the protocol is not really that realistic in a trial of this nature. This was a pragmatic trial about how intention translates into delivery in the real world. So the intention to achieve our targets was safe. I think we demonstrated no harm signal, and in that sense, the targets are safe. And I think the other really important point is the targets weren't an end in themselves, and that you know they were a lever to reduce interventions, which we absolutely achieved. And I think this point was missed a little bit by the editorialist. So I would say we showed safety of the permissive MAP target strategy, no signal for harm, a reduction in PICU length of stay in survivors, and point estimates towards benefit of the permissive MAP target group for many of the secondary outcomes and in many subgroups, so there's no reason on the face of it why our targets shouldn't be used. And remember,

remember, we didn't propose a fifth centile floor for all patients. We recommended above the fifth centile avoiding hypotension and only using our targets in the specific populations we studied. We can't comment on excluded patient groups such as cardiac or those with acute brain injury. So overall, I think it's fine to use. There's certainly nothing here which might support a more generous target, such as 50th centile or normal for age, which was proposed in some of the older guidelines. But yes, of course, you should always look at individual patient physiology. And I'm not saying a higher target is never appropriate. No, no guideline should ever be applied rigidly.

Jeff Burns *18:26*
I think you've given more context and a nuance to this, as you've noted in the presentation at Melbourne and in the JAMA article. You're conducting 12 month follow up data. When will the 12 month period be up so that we can look forward to that data?

David Inwald *18:44*
Yeah, the trial completed treatment in May of this year. So I guess we'll have the one year follow up data completed by May next year, and there'll obviously then be a period of time required to analyze that data. Now we may not have the neurodevelopmental data that perhaps people are hoping for, because really, the remaining data that we're collecting is about health economic outcomes, and quality of life, and so on. So we're not going to have very, very detailed, granular data on neurodevelopmental outcomes, which I think people might like to see, but I don't think that's that's not realistic. We're not going to have that. And what we do have is we have some PCPC/POPC data collected by bedside staff research staff asking the question about what functions like before PICU admission compared to PICU discharge. That may be the best we'll be able to provide. And that data we reported in the in the paper, and there's no difference between the groups, so that may provide some reassurance. But it's not a detailed neurodevelopmental kind of assessment.

Jeff Burns *19:57*
Understood. One of my last fundamental questions is: What lessons can the pediatric critical care community take from your findings?

David Inwald *20:04*
So I think we've shown a permissive MAP target strategy is safe. It reduces interventions. It may be associated with some benefit. Certainly, the one significant benefit was PICU length of stay and survivors. In terms of what we do in future, I think it would be interesting to look in more detail at the groups are excluded from the PRESSURE study, so the cardiac population, the brain injury population, but that would require, you know, a new study. And I suppose at some point, and if it's possible, and it may be difficult to design such a trial, it'd be very interesting to look at individualized targets. So, you know, how do we titrate therapy to flow, which I think is what we're all interested in at the end of the day.

Jeff Burns *20:49*
Well, at the Harvard Business School here in Boston, and probably at every business school across the world, I know there's a famous maxim: you manage what you measure, and the work that the UK Pediatric Critical Care Society Study group has been doing with OxyPICU and now PRESSURE. I think is just so fundamentally important because you're the ones who are looking at these assumptions that we've been operating on. We've been managing patients around the world based on previous

guidelines that, in many cases, as you noted as an author of the sepsis guidelines lacked sufficient evidence to support, and now you've really had the the courage and the wisdom to look at some of this these assumptions and say is is this relevant? I also told you when we were at the World Congress in Melbourne just several weeks ago, as you know, we had colleagues from 78 countries around the world in Melbourne, Australia, and of course they were in the room like everybody else. And afterwards, many colleagues from low and middle-income countries were really enthused because they said, you know, we all have to pay attention to what we say are the physiologic targets, regardless of the resource environment that we're in, and so I think what's so valuable about what you did was these are these are findings that are potentially generalizable across all environments. You know, obviously the resources and the therapeutic armamentarium that exist in low and middle income countries is far different than we're fortunate to have in your environment, in my environment. But nonetheless, when we declare a physiologic target, physiologic targets are universally applicable. And so they welcomed, very much welcomed your study as providing new light on you know what's the lower threshold that we should be worried about, given the inclusion and exclusion criteria in your study population. So again, just absolutely terrific work. David, I have one last question for you. If you'd be willing to share with us, what book have you read recently or in the past that really had a big impact on you?

David Inwald *23:02*
Well, my favorite medical book of all time is "A Country Doctor's Notebook" by Mikhail Bulgakov, which I don't know if you've read Jeff, but it's a fabulous book. Mikhail Bulgakov was a doctor turned author who was qualified just before the Russian Revolution, and he was sent, as many doctors were at that time, to go and work in very small hospitals in the middle of nowhere by the communists who wanted to kind of spread expertise around the country. And wrote this fabulous book, which is really just a series of vignettes of utterly kind of incredible cases that he dealt with when he was a very young, newly qualified doctor in the middle of nowhere with one assistant and very little equipment, and I really have always found that book an inspiring thing to look at and to to read those stories and to to see what good he was able to do despite the limitations of the environment he was in and with the people around him to help him. And so that's a great book to read, and I would highly recommend it.

Jeff Burns *24:07*
Well, as soon as we get off this podcast, I must confess I'm going to be looking that up. We've been speaking again with Dr. David Inwald of Cambridge University and the UK Pediatric Critical Care Society Study Group. Dr. Inwald is the first author on the clinical trial published in JAMA on September 28, 2026, entitled "Permissive Blood Pressure Targets in Pediatric Critical Care: The PRESSURE Randomized Clinical Trial." David, once again, thank you for joining us today, and most importantly, thank you for all the work you did. This was must have been a tremendous amount of work, and you've significantly advanced the science in our field. First by asking the question, and then secondly, of course, by this very very interesting study, which has left us with new ways of thinking about blood pressure targets. So, thank you so much for joining us.

David Inwald *25:00*
Thank you very much for inviting me, Jeff. And if it's okay, I just should say that this was really a huge team effort that involved the entire UK pediatric and critical care community, and ICNARC [Intensive Care National Audit & Research Centre], the clinical trials unit, and you know, obviously, all these things are achieved by a huge team and not just one person, but thank you very much for the invitation, and I'm delighted to to join you.

Sarah Marcley *25:23*
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