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GASTROSAM Key Insights: Safe Rehydration for Malnourished Kids by K. Maitland

In this World Shared Practice Forum Podcast, Dr. Kathryn Maitland discusses the findings of the GASTROSAM trial, which investigates the safety and efficacy of intravenous rehydration for children with severe acute malnutrition and gastroenteritis. The trial explores the effectiveness of intravenous fluids as a safe alternative to current rehydration guidelines for malnourished children. Dr. Maitland reviews the trial's design, key outcomes, and implications for clinical practice, providing valuable insights for healthcare professionals involved in pediatric care in resource-limited settings.

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Sarah Marcley *00:04*
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Jeff Burns *00:18*
Welcome to the World Shared Practice Forum Podcast on OPENPediatrics. I am Jeff Burns, a pediatric critical care physician at Boston Children's Hospital and Harvard Medical School. We are very pleased to have with us today, Dr Kath Maitland. Dr Maitland is professor of pediatric tropical infectious diseases at the Faculty of Medicine and Director of the ICCARE Centre at the Institute for Global Health Innovation, Imperial College London. She is based full time at the KEMRI-Wellcome program in Kenya. Kath, welcome to OPENPediatrics.

Kathryn Maitland *00:51*
Thank you. Thank you very much for having me.

Jeff Burns *00:54*
And Kath, I should say, welcome back. The last time I spoke to you was late 2011 and at that time you were visiting professor at Boston and Harvard Medical School with us, and you were also on OPENPediatrics, discussing your really now landmark paper in the New England Journal [of Medicine], published June 30, 2011 entitled "Mortality after Fluid Bolus in African Children with Severe Infection." The Fluid Expansion As Supportive Therapy (FEAST study) was designed to investigate the practice of early resuscitation with saline bolus as compared with no bolus the control, and with an albumin bolus as compared with a saline bolus in critically ill children with severe febrile illness and impaired perfusion in Uganda, Kenya and Tanzania. And what you demonstrated was that fluid boluses significantly increased 48 hour mortality in critically ill children with impaired perfusion in these resource limited settings in Africa. And I use the word paradigm shift because it truly was. It was even for those of us who don't practice in a low and middle income environment, it opened our eyes to the possibility that less might be more. But the community, if I have to say, Kath, I think was slow to catch on. I think we were slow to acknowledge it in our environment, North America, Europe, etc. But I can also say, as my hat and president of the World Federation of Pediatric Intensive and Critical Care Societies [WFPICCS], and now working closely with the WHO, the WHO themselves were slow to acknowledge these data. And it wasn't until 2020 that the current WHO guidelines on resuscitating children in this context really acknowledged your findings and have adjusted the approach to fluid resuscitation. So, you know, I have to, you know, salute you again for that work that you did now 14 years ago, and you're here today because 14 years later, you're publishing in the New England Journal [of Medicine] again you published

your study entitled "Intravenous Rehydration for Severe Acute Malnutrition with Gastroenteritis", and you're here today because we'd like to talk to you about that study and what the motivation was for that study and what you found. And so Kath, if I could turn this now to you, what was the motivation for your study that I believe you refer to it as the GASTROSAM trial. What was the motivation for the trial? What research gap was it trying to address?

Kathryn Maitland *03:38*
Thank you. So I think I just want to put this first of all in the context of gastroenteritis worldwide, because I think that for most people, they won't see children dying of gastroenteritis. There are approximately 2.5 billion cases worldwide in children under five. It is the second biggest killer, and most of those deaths will occur in low to middle income countries. So for children who come into hospital with gastroenteritis, they're eight and a half times more likely to die than children who don't have gastroenteritis. So that's telling you that this is a this is a big killer of children. And we looked at the guidelines worldwide of who's doing research in this area, and this really is the silent emergency, because worldwide, there has been no clinical trials in lower to middle income countries looking at the current recommendations. And only three studies at trials have been conducted, and none of those have mortality so completely not relevant to our context. So that's the global context, just of gastroenteritis, narrowing down to children with severe malnutrition, they frequently are admitted to hospital, and about half them will present with diarrhea or gastroenteritis. Their mortality is awful. Overall mortality is around about 15 to 20% but if they're complicated with severe dehydration and gastroenteritis, that can go up as high as 40 to 50% so the outcome is absolutely dreadful. And what you know, what are the current recommendations for these children. If children who don't have malnutrition, that the children who are managed for severe gastroenteritis, they normally are assessed to have approximately 10% dehydration. So that's 100 mils per kilo, and they're recommended to give that. It's called Plan C. It's a very, very complicated two stage process, two different rates for two different age groups. If that's the plan has to be given 100 mils per kilo over a short, short period of time, between four and six hours. Remember, in the FEAST trial, we only give 20 mils per kilo, so that's a very, very liberal rehydration protocol. But if you don't have malnutrition they recommend do not put an IV line in. Why do they recommend that? In the words that children are recommended not to have IV rehydration, instead, they're recommended to have oral rehydration. The major concern is that people have viewed children with severe malnutrition. There's two different phenotypes. There's the severely wasted one, where children are bone thin, you know, huge lack of muscle mass, or the edematous type, often they coexist. Edematous test type called kwashiorkor. And both types are thought to be prone to heart failure, so they feel that it's too unsafe to give intravenous fluids to these children, including shock, etc, and they should not receive IV fluids, but only if they develop severe shock. So currently, they're recommended to receive a low osmolarity, low sodium solution. It's a specific oral rehydration solution that's been made for children with malnutrition, and they say that this can only be given in a health facility. That meaning that it cannot be given in the community. So if you want to give any rehydration at all to a child who's got severe malnutrition, you've got to get them into the health facility. And this is probably some of the reasons why they've got an appalling outcome, because they obviously coming in late with no pre management, and even when they're in there. So this was something after FEAST we said we have to tackle. And we've basically layered upon layer. Before the trial started, we had to sort of say, you know, is there evidence behind, you know, the fact there is a very, very strong belief, and this is very, very widely taught. It's one of the first things people are taught about children with severe malnutrition, about heart failure and incipient heart failure. Well, we looked for the evidence, and it really wasn't there. So we did studies about 250 overall, between Kenya and

Malawi, two separate studies that actually looked at myocardial function, and we found that it was actually normal. And in our the study that we did in Kilifi, in Kenyan children, published in JAMA [Journal of the American Medical Association] Open in 2019 called CAPMAL, we actually showed that children had normal responses to fluids. In other words, their Starling curves responded in the same way that would do if they'd had boluses elsewhere. So we were fairly confident this was, you know, should be, you know, sort of the WHO should act upon this. But really, the guideline that's been in place for 26 years has not changed. So still, children with severe malnutrition are, I shouldn't say it, but because that sounds like loss, loss of equipoise, but they are denied intravenous rehydration because it's felt this is so dangerous to give it to children. So that's very high mortality, very, very low evidence base, based on expert opinion this, this guideline, needed addressing. And in the 26 years that you know, a definitive phase three trial has not been undertaken specifically in Africa.

Jeff Burns *09:18*
Well, Kath, that was a beautiful description of the problem as it exists, really, around the world, as well as, course, in low and middle income environments. So could you tell us a little bit about your trial design, and where did you undertake this trial?

Kathryn Maitland *09:34*
Thank you. So the GASTROSAM trial was designed as a multicenter investigator led individually randomized trial. It was registered before we started enrolling, and the protocol has been published. The trial design obviously, we have to go back to the starting box to say, well, you know, we can't just make up a volume of fluid to give these children. We have to sort of stick with something that's already there. So we're saying there's a distinction between children who don't have malnutrition and children who do have malnutrition. So that's the starting block for the intervention arm. So we wanted to compare what's currently standard of care, which is control oral rehydration, versus a liberal rehydration. But from what we learned in FEAST, we were quite anxious about pouring. So you have a rapid phase, which is given over half an hour or an hour, which is 30 mils per kilo from and that's even if after they've had shock. So we were concerned about that. And so our other experimental arm was a slow rehydration. So I'm going to go through those three arms now, so the control was, as I said, that's oral rehydration with this ReSoMal solution, where children were given about eight to 10 hours, about 100 mils per kilo, oral. They were only allowed intravenous fluids if they developed shock. And shock was quite extreme, so it had to have, I think, three features of impaired perfusion. So that's that intervention arm. For the second intervention arm, this is the WHO Plan C. So that's what we call liberal rapid. So it's a rapid, so it's first of all, the children were assessed for shock. If they had shock, they had a bolus of fluid, and then they went on to have their rehydration between four to six hours, depending on whether you were under one year of age or over one year of age. That I'm telling you, it was very, very difficult to teach. People couldn't do it. We had to have perfusers to make them do it so they could follow this and the nurses were backing to the perfusers to making sure that they were doing the right rates. And then we have this slow, a liberal rehydration arm. And that was just 100 mils per kilo, no boluses at all, even if they had shock you went straight on to receiving your just your rehydration therapy, and that was given over eight hours at an even rate. So that's the three intervention arms. I didn't say who were incorporated in the trial, clearly, children who had severe acute malnutrition and they had quite severe diarrhea over three loose stools, and then severe dehydration, which is any of three signs of severity of dehydration. Initially, the trial took place in East Africa, and it was in four sites there. Two sites in eastern Uganda and two sites on the coast of Kenya. These sites represented areas where you have stable under nutrition in the community, which then switches quite rapidly into severe

malnutrition when they've usually when they've had a clinical illness or a clinical event that switches, that sort of brings them into there. So you see malnutrition all year round. Later in the trial were brought in just so we could complete the trial. Numbers were the huge sites in West Africa, in Niger and Nigeria, both of those sites are in the humanitarian context. They were both being run by Médecins Sans Frontières, or what you would call Doctors Without Borders. They have a seasonal malnutrition where you have huge numbers coming into these clinics. It's the the Sahel hunger gap, and where you have kids pouring into these enormous refugee camps. And you know, being able to manage these children, obviously, is the burden of those is just a massive undertaking. And that's what Médecins Sans Frontières do very well. So the context, again, in which the trial was run is that they were generally managed on the general pediatric wards in the eastern Uganda sites, whereas in the Niger and Nigeria sites, they were managed on what we call a high dependency care unit, where you you didn't have access to mechanical ventilation, but you had a very, very close you had a team around you that gave you 24 hour care. And also very, very sort of all the other supportive care that you could get in the context of a sort of high dependency care unit. I will tell you a little bit about the challenges a bit later, but that's that's really the design and the trial characteristics of the site. Just wanted to say that all children received standard of care. So there was, apart from the randomizations of the oral and liberal rehydrations, they all got the same standard of care. So they got a package of care. And we then monitored the children very closely, because of the concern that we were going to put these children into heart failure. So every 30 minutes for two hours, then hourly for eight hours, and then at 12 hours and 24 hours there afterwards and doctors, when had to go to the bed each these time points, they had to go and look at the patients. Obviously, they have to have the whole range of bedside monitoring done, but also actively solicited signs of fluid overload. They'd all been taught how to do this and these were recorded at each review, and all of the data was collected onto standard forms. So yes, and we had external oversight by data monitoring committees, who were the only people looking at the data over the time points and the trial steering committee.

Jeff Burns *15:49*
Well, Kath sitting here in Boston, North America, our problems seem quite far remote and somewhat insignificant compared to the chronic malnutrition that you just described in your East Africa sites and the episodic and devastating malnutrition that you see in your West Africa sites. Could you tell us about the outcomes that you were trialing and what were your key findings?

Kathryn Maitland *16:17*
Okay, so the primary outcome was mortality at 96 hours, and we had secondary outcomes of mortality to day 28 and a number of anthropometric outcomes, change of weight, mid upper arm circumference at day three and day seven. Important in this trial were the safety endpoints. This trial was about safety. So those were the headlines and secondary and safety endpoints were evidence of pulmonary edema or heart failure, but also the development of shock and particularly, obviously, thinking about the oral rehydration arms. We had a number of biochemical endpoints, change in sodium at 24 hours after the completion of intravenous rehydration. The reason why we had that is there's the additional concern. Not only they're concerned about the children are prone to fluid overload. It is said in the guidelines, we have not been able to find any evidence why, but children with severe malnutrition cannot cope with a sodium load. That's the additional rationale for not giving them sodium rich solutions. So we wanted to see whether there was, you know, issues sort of over giving them the hypernatremia as a result of our giving them sodium rich solutions. And our main comparison, when I present the results, is it's liberal versus control. So when you're looking at the numbers in the sort of statistics, the major comparison is

liberal versus control. Although we did secondary analysis over the different types of liberal versus control, the main outcome was liberal versus control. So just going on to the results, were these children that came into the trial, I think important to highlight in the baseline. These were very, very sick children. Child who has a normal anthropometric indices, weight for height, Z score would be around two or three if he was normal. These children had that height for weight Z scores of almost minus five. These were horrifically undernourished children. Quite a number of them had been in previously admitted for malnutrition. Although their median age was around 12 to 14 months, many had very, very poor appetite. They were unable to retain any oral fluids, about 80%. Altered consciousness was very prevalent, about 40%, 30 to 40%. We found that in their biochemical measures at baseline, 53% had very severe hyponatremia. That's a sodium below 125 millimoles. I think you probably rushed somebody to an ICU if you saw something like that in your setting. Also of note, 40 to 50% of children had severe hypokalemia that that is a potassium less than 2.5 millimoles per liter. Up to about 12% had a positive blood culture. Most of those positive blood cultures was gram negative bacteremia. So just to highlight that, these are very, very sick children. These are all high risk factors for very poor outcome, as we've previously seen. So during the trial, the adherence was absolutely excellent. Everybody adhered to the randomization. This was a result of us all sitting down at the beginning and saying, if we run this trial badly, and you go with what you believe rather than following the protocol, then what we'll come up with is a mess at the end, and we won't be able to publish it. And that will be all of those children that said that they were going to go into the trial. You know, you've not done them any service. So people absolutely adhered to the protocol. So that means the results are credible. We had a very, very high retention rate, meaning that we we didn't have to do a [mins per] protocol analysis for both of those reasons. Fluids were started on the IVs in the pooled liberal arms within 14 minutes of them being randomized. So they got their fluids and they got the right volumes. What we did see for the children who were in the oral arm at the beginning, nearly 10% needed a bolus of fluid because they were in shock. Another, quite another number afterwards also have to be corrected for shock. But also in that oral arm because they were still profusely vomiting, 93% had to have a nasogastric tube inserted effectively for nearly all of them to actually receive their intervention. If we go to the primary and secondary endpoints, the primary endpoint mortality at 96 hours overall, there was no difference from the control to the pooled liberal. The control was 8% and the pooled liberal was 7% this is at 96 hours. So there's obviously the statistics show there was no difference between those arms. There's similar mortalities between 12 and 10% overall at day 28. We saw a much higher urine output in the liberal arms versus the control, which is probably not unexpected. The number in the control arm who developed a serious adverse event, although numerically higher than the other arms, it wasn't statistically higher. And although we were giving very, very rapid rehydration to these children, we were concerned about their neurological whether they developed any neurological events, we didn't see any. Numerically, more children in the control arm developed shock after the start of their intervention. So when we actually look at the safety outcomes again, this trial was about safety, we saw in all of the children in the trial, no episodes of pulmonary edema and no episodes of heart failure. And this is not because the doctors weren't trained how to do this. They were all trained in the same and then they were we didn't see any episodes, which was very reassuring for safety. We saw a better time for correction of hyponatremia in the liberal arms versus the control but we didn't see, I mean, only 2% overall, and this was the same across all of the arms developed hypernatremia, which, again, was another concern about giving sodium rich intravenous fluids. So our conclusions were that while we had a no difference in mortality at 96 hours, we might have felt deflated about that, but we have to almost celebrate that, the fact that these children were so well looked after that we in general, brought down mortality from what we'd expected to be around about 40%, down to six to 9% and that was really

because it shows the value of actually being enrolled in a clinical trial, but it was also due to the increased levels of staffing and the quality of care that they provided. The bundle of care that they were given, and that adverse events were quickly picked up and also then managed. But reassuringly, we saw no evidence of fluid overload, which is an enormous step forward.

Jeff Burns *23:56*
Well, Kath, it's fascinating to hear you describe the results of your trial. And I must confess, I'm sitting here thinking to myself, which outcome is it? [Does] your trial prove that there is no harm in intravenous hydration, as was the dogma, as you noted prior to your trial, and that intravenous hydration, as you administered it in that environment, is as efficacious as oral rehydration. Or, is the message from your trial, in your view, that oral rehydration continues to be effective, and certainly as effective as intravenous hydration as you administered it, and therefore, because it's a less complicated and likely more available, obviously, method of rehydration that oral rehydration remains the primary focus in your environment. Which outcome, which interpretation do you take from your study?

Kathryn Maitland *25:01*
Yes, thank you. I mean, some people may be reassured that oral was as good as intravenous but I think you have to look at how we run this trial. We ran this trial because ethics required us to be almost at the bedside during the entire time when the children were receiving their oral rehydration or intravenous rehydration. That, in reality, just simply could not happen. We're looking at busy pediatric wards whose bed capacity is often two or sometimes two and a half times over subscribed, where you have few staff, and giving oral rehydration, they indicated that it might be need to be given by a nasogastric tube, but this is the first indication that in order to make oral rehydration effective, that you have to literally be by the bedside and administer it and through a nasogastric tube, which is not easy to. It has to be checked each time you administer the next dose of oral rehydration solution. And it's not without its own dangers. It was done safely because we had a dedicated team. We asked all of the teams in a meeting afterwards, you know, what would you prefer? And they all said, gosh, intravenous, the slow arm, because it's just so easy. There's just little sort of calculation you have to do at the beginning, and just and then let it run. Obviously you have to go and check the child. But if, if you're thinking of this the context, then that is the simplest option. Again, we saw across all arms, no evidence that this caused fluid overload, and continuing to recommend oral rehydration, from all that we have learned in the GASTROSAM study. So this was also a demonstration of how not to make a guideline, and thinking it was simple, but it's also has implications beyond that, because it is not recommended that children with severe malnutrition in the community, and many do get managed in the community, they should not have oral rehydration solution, because you've got to get to hospital to get that in orally. So again, it's, yeah, it's means that probably more children die than is necessary. This was an overall demonstration of the safety of a more a standard way of giving rehydration, I think.

Jeff Burns *27:51*
Kath, where do we go next? Do we need more trials like yours to convince policymakers, et cetera? Where do we go next with this?

Kathryn Maitland *28:04*
I think we don't need any more trials. The guideline was put in place to protect children with malnutrition from people giving them IV rehydration which would cause them harm. We have demonstrated it is not harmful. We've also demonstrated the huge challenges of giving oral rehydration solutions they hadn't

anticipated the high number requiring nasogastric tubes, 90%. That 22% needed boluses because they were in shock or developed shock. I think we desperately need to simplify rehydration guidelines for children in resource limited settings, and that there should be no distinction between those who are well nourished and those who are malnourished.

Jeff Burns *28:50*
Well, Dr Kath Maitland, it's a privilege to have you back on OPENPediatrics 14 years after your FEAST study, and we've been discussing with you your trial, published in the June 13, 2025, issue of the New England Journal of Medicine entitled "Intravenous Rehydration for Severe Acute Malnutrition with Gastroenteritis". Kath, it's late in the afternoon for you in Kenya, but on behalf of all of our colleagues around the world, I just have to say that we are extremely grateful that in our community, we have someone like you who's doing this research on things that really matter. And so Kath, keep going. We look forward to your next trial and your next podcast on OPENPediatrics. Thank you for joining us today.

Kathryn Maitland *29:38*
Thank you that is very sweet of you. I feel quite humbled.

Sarah Marcley *29:44*
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